# GUIDANCE DOCUMENT FOR CELL, TISSUE AND ORGAN ESTABLISHMENTS

## Safety of Human Cells, Tissues and Organs for Transplantation

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**Health Products and Food Branch**
**Guidance Document**

Canada

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| Our mission is to help the people of Canada maintain and improve their health.<br>Health Canada | HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by:<br>• Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,<br>• Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.<br>Health Products and Food Branch |

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## FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy and/or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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# Introduction

The Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations or Regulations) contain safety requirements with respect to processing; storage; record keeping; distribution; importation; error, accident and adverse reaction investigation and reporting. Processing includes donor screening, donor testing, donor suitability assessment, retrieval (except in the case of organs and islet cells), testing and measurements performed on the cells, tissues or organs (CTO) after they are retrieved, preparation for use in transplantation (except for organs), preservation, quarantine, banking, packaging and labelling. These Regulations are intended to result in improved protection of the health and safety of Canadian transplant recipients.

The CTO Regulations are administered by the Biologics and Genetic Therapies Directorate, Health Products and Food Branch, Health Canada. Any questions concerning the Regulations themselves or this guidance document can be sent to this email address: hc.bgtd.opic-bpci.dpbtg.sc@canada.ca

## Policy Objectives

The purpose of this regulatory framework is to minimize the potential health risks to Canadian recipients of human CTO. This guidance document provides an interpretation of the CTO Regulations.

## Scope and Application

The CTO Regulations apply only to human CTO which are to be used in transplantation. CTO donated for different purposes, such as for education or non-clinical research, are not within the scope of these Regulations.

In this guidance document, both the scope of the CTO Regulations as well as the activities they govern are outlined. It is intended to be an important point of reference: it will help readers determine whether a product and the activities related to it are governed by the CTO Regulations, and give more details as to what requirements must be fulfilled. The requirements that are discussed in this document are the current safety requirements for CTO used in transplantation. This guidance document supersedes previous documents.

The CTO Regulations apply to all individuals and establishments that handle, process, distribute or import human organs, or minimally manipulated cells and tissues for homologous use, for transplantation in another individual in Canada. In order to fully comprehend these Regulations, the Food and Drugs Act (F&DA) as well as the most updated version of the National Standard of Canada entitled Cells, Tissues, and Organs for Transplantation and Assisted Reproduction (National Standard), published by the Canadian Standards Association (CSA), must also be consulted.

It is the responsibility of the establishment to ensure that they have access to the most recent updated version of the CTO Regulations, the National Standard incorporated by reference into those Regulations and this guidance document.

## Background

The purpose of this regulatory initiative is to minimize the potential health risks to Canadian recipients of human CTO. These Regulations establish safety requirement relating to the processing and handling of these products, resulting in improved protection of the health and safety of Canadian transplant recipients.

The CTO Regulations are based on the National Standard as well as information obtained during extensive consultations with the provinces, territories and transplantation experts. They were developed using a risk management approach. The National Standard has been made available as a model for other nations through international regulatory cooperation.

The CTO Regulations directly reference sections of the General Standard CAN/CSA Z900.1, entitled Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements, along with four of the five subset standards for specific organ and tissue types (i.e. the standards for lymphohematopoietic cells, perfusable organs, tissues, and ocular tissues), thus making them mandatory. It is important to note that the National Standard speaks to various aspects of the donation and transplantation process. However, as Health Canada's scope with respect to CTO is limited to activities related to product safety and quality assurance, every section of the National Standard that is referenced in the CTO Regulations is related to the safety or quality of CTO. Sections of the National Standard that relate to the practice of medicine are not referenced in these Regulations, as practice of medicine does not fall under federal jurisdiction.

The CTO Regulations set out safety requirements with respect to processing; (which includes donor screening, donor testing, collection/retrieval, preservation, packaging, labelling, quarantine); storage; record keeping; distribution; importation; error, accident and adverse reaction investigation and reporting. The objective of these Regulations is to maximize the safety of CTO, by clearly stipulating the safety requirements adopted from the National Standard, thus making them mandatory. Referencing the National Standard provides a consistent and safety-focussed regulatory framework that will minimize the risks to Canadian recipients of CTO.

## CSA Group National Standard

The Z900 package of the National Standard may be obtained by calling 1-800-463-6727 or may be ordered from the CSA Group web site. Since the CTO Regulations are standard-based, all CTO establishments that are required to comply with sections of the Regulations referenced in the National Standards will need to possess the most updated version of the National Standards, in order to have access to the latest regulatory requirements. These Regulations incorporate by reference the applicable standards as amended from time to time. Amendments to the National Standards will be sent to establishments that have registered their package with the CSA Group. For more information on how to register your National Standards and receive updates, refer to the CSA Group Standards Update Service page of the standards.

Due to the fact that the field of CTO transplantation continues to change as the science evolves, Health Canada has chosen to base their regulatory framework on standards. The National Standard was developed by a committee of transplantation experts and interested stakeholders in a consensus driven process that may enhance future compliance.

All stakeholders play a key role in keeping the standards up-to-date. Each subset of the CSA Group National Standard contains a Proposal for Change Form, which may be used by stakeholders to submit proposals for change directly to the CSA Group. The CSA Group has recommended that the following information be supplied, in addition to the appropriate contact information, in order to facilitate the evaluation of the proposed changes:

- standard/publication number
- relevant Clause, Table, and /or Figure number(s)
- wording of the proposed change
- rationale for the change.

## Acronyms

| | | | |
|---|---|---|---|
| CMV | Cytomegalovirus | EBV | Epstein-Barr Virus |
| CSA | CSA Group | F&DA | Food and Drugs Act |
| CTO | Cells, Tissues and Organs | F&DR | Food and Drugs Regulations |

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|---|---|
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| HLA | Human Leukocyte Antigen |
| HTLV | Human T-Lymphotropic Virus |
| MDALL | Medical Devices Active Licence Listing |
| MDR | Medical Devices Regulations |
| RORB | Regulatory Operations and Regions Branch (Formerly Health Products and Food Branch Inspectorate) |

## Guidance for Implementation

In this guidance document, the word "should" indicates a recommendation made by Health Canada. Where standards are recommended, decisions regarding their implementation should be based on a risk benefit analysis within the context of the establishment's operations. It should also be noted that the CTO Regulations specify minimum safety standards that may be exceeded by CTO establishments.

The statements enclosed in the boxes, as well as the definitions below and the labelling requirements tables under sections 30 to 32 are sections taken directly from the CTO Regulations.

## Interpretation (Section 1 of the CTO Regulations)

Definitions
**1.** The following definitions apply in these Regulations.

This section is a glossary of terms used in the CTO Regulations. All definitions that are found in section 1 of these Regulations can be found here.

"accident"
"accident" means an unexpected event that is not attributable to a deviation from the standard operating procedures or applicable laws and that could adversely affect the safety of a transplant recipient or the safety, efficacy or quality of cells, tissues or organs.

"Act"
"Act" means the Food and Drugs Act.

"adverse reaction"
"adverse reaction" means an undesirable response in the recipient to transplanted cells, tissues or organs, including the transmission of a disease or disease agent.

"banked"
"banked", with respect to cells and tissues, means processed cells and tissues that have been determined safe for transplantation and that are stored by the source establishment in its inventory and available for distribution or transplantation.

"cell"
"cell" means the fundamental biological unit of a human organism that is for use in transplantation.

"distribute"
"distribute" does not include to transplant.

"donor"
"donor" means a living or deceased person from whom cells, tissues or organs are retrieved.

"donor assessment record"
"donor assessment record" includes the donor screening, any available donor testing results, information obtained from the donor's medical records and a copy of the donor consent.

"donor identification code"
"donor identification code" means the unique numeric or alphanumeric designation that is assigned by the source establishment to a donor under section 56 and that associates each cell, tissue and organ, or part of one, to that donor.

"donor screening"
"donor screening" means an evaluation based on the donor's medical and social history and physical examination, the results of any diagnostic procedures performed, and, if applicable, the autopsy.

"donor suitability assessment"
"donor suitability assessment" means an evaluation based on the donor screening and

(a) in the case of lymphohematopoietic cells, tissues and organs retrieved from live donors and of tissues retrieved from deceased donors, all donor testing results; and
(b) in the case of fresh skin, islet cells and organs retrieved from deceased donors, the donor testing results that are necessary at the time of transplantation.

"donor testing"
"donor testing" means the laboratory tests and measurements done on a donor or donor specimen to determine all of the following:

(a) whether the donor has or ever had a transmissible disease or is or ever was infected with a transmissible disease agent;
(b) donor compatibility; and
(c) the degree of functionality of the cell, tissue or organ that is to be retrieved.

"error"
"error" means a deviation from the standard operating procedures or applicable laws that could adversely affect the safety of a transplant recipient or the safety, efficacy or quality of cells, tissues or organs.

"establishment"
"establishment" means a person, a partnership or an unincorporated entity, or a part of any of them, that carries out any of the following activities in respect of cells, tissues or organs:

(a) importation;
(b) processing;
(c) distribution; and
(d) transplantation.

"exceptional distribution"
"exceptional distribution" means the distribution under sections 40 to 42 of cells, tissues or organs that have not been processed under these Regulations.

"exterior label"
"exterior label" means the label that is affixed to the exterior package.

"exterior package"
"exterior package" means the outermost package in which a cell, tissue or organ is delivered, transported or shipped.

"general standard"
"general standard" means National Standard of Canada CAN/CSA-Z900.1 entitled Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements, as amended from time to time.

"homologous"
"homologous", in respect of a cell, tissue or organ, means that the cell, tissue or organ performs the same basic function after transplantation.

"interior label"
"interior label" means the label that is affixed to the interior package.

"interior package"
"interior package" means the innermost package of a cell, tissue or organ that has a non-sterile exterior.

"lymphohematopoietic standard"
"lymphohematopoietic standard" means National Standard of Canada CAN/CSA-Z900.2.5 entitled Lymphohematopoietic Cells for Transplantation, as amended from time to time.

"medical director"
"medical director", in respect of an establishment, means a physician or dentist who is licensed under the laws of the jurisdiction in which the establishment is situated to provide health care or dental care and who is responsible for the application of the standard operating procedures and for all medical or dental procedures carried out there, as the case may be.

"minimally manipulated"
"minimally manipulated" means

a) in respect of a structural tissue, that the processing does not alter the original characteristics that are relevant to its claimed utility for reconstruction, repair or replacement; and
b) in respect of cells and nonstructural tissue, that the processing does not alter the biological characteristics that are relevant to their claimed utility.

ocular standard"
"ocular standard" means National Standard of Canada CAN/CSA-Z900.2.4 entitled Ocular Tissues for Transplantation, as amended from time to time.

"organ"
"organ" means a perfusable human organ for use in transplantation, whether whole or in parts, and whose specific function is intended to return after revascularization and reperfusion. It includes any adjunct vessels that are retrieved with the organ for use in organ transplantation.

"organ standard"
"organ standard" means National Standard of Canada CAN/CSAZ900-Z900.2.3 entitled Perfusable Organs for Transplantation, as amended from time to time.

"package insert"
"package insert" means the document that is prepared by the source establishment to accompany a cell, tissue or organ.

The expression "prepared by the Source Establishment" used in the definition of "Package Insert" may also refer to the package insert being prepared by an establishment in accordance with the Standard Operating Procedures.

"processing"

"processing", in respect of cells, tissues and organs, means any of the following activities:

- (a) donor screening;
- (b) donor testing;
- (c) donor suitability assessment;
- (d) retrieval, except for organs and islet cells;
- (e) testing and measurements performed on the cells, tissues or organs after they are retrieved;
- (f) preparation for use in transplantation, except for organs;
- (g) preservation;
- (h) quarantine;
- (i) banking; and
- (j) packaging and labelling.

### Retrieval

Under the CTO Regulations, a source establishment is responsible for the retrieval of cells and tissues. In the case of organs, retrieval is **not** considered processing, and thus is not the responsibility of the source establishment. Organ retrieval is a surgical procedure carried out in a manner that is adapted to the donor organ and the needs of the recipient, and is considered to be within the domain of medical practice. As Health Canada does not regulate medical practice, the retrieval of organs and islet cells is exempt from the definition of processing. For instance, the actual retrieval of a pancreas for further processing is exempt from the definition of processing, whereas the activities associated with isolating the islet cells are captured under the definition of processing (since they are considered preparation for use in transplantation).

### Post-retrieval testing and measurements performed on the cell, tissue or organ after it is retrieved

This includes but is not limited to bacteriological testing and biopsy results of the cells, tissues and organs, if performed.

### Preparation for use in transplantation

Source establishments are responsible for the preparation of cells and tissues for use in transplantation, other than final preparation done by the transplant program at the time of transplantation. Examples of preparation of cells and tissues may include cutting/sizing, dissecting, centrifugation, lyophilisation and irradiation. The depletion of plasma and red blood cells from lymphohematopoietic cells, as well as activities that are part of the processing of lymphohematopoietic cells prior to cryopreservation, are also included in the preparation for use before transplantation. The preparation of organs for use in transplantation is **not** considered processing, and thus is not the responsibility of the source establishment. As previously stated for retrieval, the preparation that an organ undergoes for use in transplantation is adapted to the donor organ and the needs of the recipient, and thus is considered to be within the domain of medical practice. As Health Canada does not regulate medical practice, the preparation of organs for use in transplantation is exempted from the definition of processing and the related requirements under these Regulations.

As previously mentioned, the actual retrieval of a pancreas for further processing is exempted from the definition of processing, whereas the activities associated with isolating the islet cells are captured under the definition of processing (since they are considered preparation for use in transplantation). Apart from this one distinction, islet cells are regulated according to the same criteria as organs (i.e., the same donor screening and testing requirements apply to organs and islet cells).

## Preservation

Preservation (e.g., cryopreservation, lyophilisation, etc.) refers to the act or process of preserving cells and tissues, or keeping them from deterioration or decay prior to their use in transplantation.

## Banking

Banking in the context of these Regulations refers to the storing of processed cells and tissues (including adjunct vessels that are not used immediately for transplantation with the organ with which they were distributed) **by a source establishment** once these cells and tissues have been processed in accordance with the Regulations.

Cells and tissues that are stored by an importer for further distribution or by an end user establishment for transplantation after the source establishment has released the cells and tissues from their inventory are not considered banked.

In the case of lymphohematopoietic cells collected from bone marrow or peripheral blood, any storage of the cells is not considered banking if the donation is reserved for the treatment of a designated recipient.

"quality assurance system"
"quality assurance system" means the co-ordinated activities of an establishment that relate to the safety of cells, tissues and organs. It includes

- (a) the standard operating procedures;
- (b) records to demonstrate that the standard operating procedures have been implemented; and
- (c) audit processes to verify that the standard operating procedures are being implemented.

"scientific director"
"scientific director", in respect of an establishment, means an individual who is responsible for the application of the standard operating procedures and for all technical procedures carried out there.

"serious adverse reaction"
"serious adverse reaction" means an adverse reaction that results in any of the following consequences for the recipient:

- (a) their in-patient hospitalization or its prolongation;
- (b) persistent or significant disability or incapacity;
- (c) medical, dental or surgical intervention to preclude a persistent or significant disability or incapacity;
- (d) a life-threatening condition; and
- (e) death.

"source establishment"
"source establishment" means

- (a) subject to paragraph (b), in the case of an organ from a deceased donor, the relevant organ donation organization;
- (b) in the case of adjunct vessels that are retrieved with an organ and not used immediately in the organ transplantation, the relevant tissue bank;
- (c) in the case of an organ from a living donor or lymphohematopoietic cells that are not banked, the relevant transplant establishment;
- (d) in the case of tissues or banked lymphohematopoietic cells, the relevant cell or tissue bank; and
- (e) in the case of islet cells, the establishment that prepares the cells for use in transplantation.

"standard operating procedures"
"standard operating procedures" means the component of the quality assurance system that comprises instructions that set out the processes and procedures to follow in carrying out the activities of an establishment.

"tissue"
"tissue" means a functional group of human cells for use in transplantation. It includes the cells and tissues listed in the definition "tissue" in section 3.1 of the general standard, except for paragraphs (g) and (l).

"tissue standard"
"tissue standard" means National Standard of Canada CAN/CSA-Z900.2.2 entitled Tissues for Transplantation, as amended from time to time.

"transplant"
"transplant" means to implant cells, tissues or organs into a recipient.

### Additional definitions for the purpose of this guidance document

"Importer" means an establishment that brings in or facilitates the transfer of CTO from a foreign source located geographically outside Canada and further distributes it to CTO establishments in Canada. Health Canada does not consider an establishment to import if the CTO is from inside Canada (i.e., from a different province or territory). If an establishment is solely shipping the CTO on behalf of an importer then the shipping company does not have to register as an importer (e.g. FedEx).

"Establishment that distributes as an intermediary" means an establishment that facilitates the further distribution of CTO determined safe for transplantation by a source establishment from one establishment to another.

"Retrieval establishment" means the organization affiliated with the physical building in which the retrieval takes place. The retrieval team is not necessarily affiliated with the retrieval establishment.

## Application (Sections 2 & 3 of the CTO Regulations)

Scope of Regulations
**2.** These Regulations apply only to organs and minimally manipulated cells and tissues.

Cells and tissues can be manipulated by varying degrees, which ranges from minimally manipulated cells and tissues (e.g., ocular tissue, fresh frozen tissues, etc.) to more than minimally manipulated cells and tissues (e.g., cells subject to ex-vivo expansion, differentiation, recombinant DNA technology, etc.).

CTO used for transplantation are generally retrieved from a donor in a functional state, and are expected to maintain the same function in the recipient, provided that measures are taken to preserve their integrity and function during processing. Since the CTO Regulations are based primarily on safety, and do not contain requirements for the evaluation of clinical effectiveness, they are considered adequate only for those tissues that are minimally manipulated, and consequently, are more likely to maintain their integrity and function during processing.

A minimally manipulated structural tissue, as defined in section 1 of the CTO Regulations, must still possess the characteristics that enables it to carry out the function of reconstruction, repair or replacement. Therefore, the separation of the structural tissue into components whose characteristics relating to reconstruction, repair or replacement are not altered is considered minimal manipulation. Similarly, the extraction or separation of cells from structural tissue, in which the remaining structural tissue's characteristics relating to achieving reconstruction, repair or replacement were unaltered, would also be considered minimal manipulation. Other examples of procedures that would be considered to be minimal manipulation include cutting/sizing, dissecting, grinding and shaping; disinfection by soaking in antibiotic solution; sterilization by ethylene oxide treatment or gamma irradiation; cell separation; lyophilisation; and preservation (e.g. cryopreservation, freezing, cooling, chemical preservation).

In order to be considered minimally manipulated, and therefore be included in the scope of the CTO Regulations, the structural tissue must not have undergone processing **that alters the original characteristics that are relevant to the claimed utility of the product for reconstruction, repair or replacement.** A tissue characteristic is "original" if it is present in the tissue in the donor; and it is "relevant" if it could have a meaningful bearing on how the tissue performs when utilized for reconstruction, repair or replacement.

A minimally manipulated cell or non-structural tissue must still possess the biological characteristics (and thus potentially the function or integrity) that are relevant to their claimed utility. At this time, examples of processing that are considered to be minimal manipulation include cell separation techniques such as density gradient separation, selective removal of B-cells, T-cells, red blood cells or platelets, cell selection to enrich the product with CD34+ cells, and centrifugation. Other processes considered minimal manipulation include lyophilisation; cryopreservation; and freezing. It should be noted that enzymatic digestion of a pancreas to dissociate islet cells prior to isolation is currently considered minimal manipulation because it has already been demonstrated in clinical trials that these cells maintain their biological function. Establishments must notify Health Canada before subjecting islet cells to further manipulation prior to transplantation (e.g., cell expansion, the addition of drugs, hormones, or cytokines). Health Canada must also be notified prior to employing enzymatic digestion for the isolation of other cell types. Appendix 1 contains a decision tree that can help in determining if a cell or tissue falls under the scope of the CTO Regulations.

It is recognized that in some cases, it may be difficult to classify cells and tissues as minimally manipulated or more than minimally manipulated and decisions will have to be made case by case, based on a review of the manufacturing process and/or the availability of clinical data to support their intended use.

Inquiries pertaining to the classification of CTO can be sent to Health Canada through the following email address: hc.bgtd.opic-bpci.dpbtg.sc@canada.ca.

For the purpose of determining which CTO are subject to these Regulations, minimally manipulated cells and tissues could be classified further based on other criteria. For example, in order to be included in the scope of these Regulations, minimally manipulated tissues must not meet any of the criteria specified in Section 3 of the CTO Regulations. Thus, these Regulations apply to only those minimally manipulated cells and tissues that meet **all** of the following criteria:

a) they must be intended for allogeneic use, which includes CTO donated for use by relatives of the donor;
b) they must be intended for homologous use (i.e., they are intended to perform the same function in the recipient as they did in the donor);
c) they must not have a systemic effect and depend on their metabolic activity for their primary function, with the exceptions noted in subsection 3(1)(d) of these Regulations;
d) they must not be combined with non-cell or non-tissue products, such as artificial elements used for tissue engineering;
e) their safety and effectiveness must have been established through historical use or clinical studies.

It should be noted that autologous CTO are not within the scope of the CTO Regulations. They are not, for this reason, discussed further in this guidance document.

Non-application — various therapeutic products

**3.** (1) These Regulations do not apply to any of the following therapeutic products:

(a) cells, tissues and organs that are for non-homologous use;
(b) cells, tissues and organs that are for autologous use;
(c) heart valves and dura mater;
(d) tissues and cells — except for islet cells, and except for lymphohematopoietic cells that are derived from bone marrow, peripheral blood or cord blood— that have a systemic effect and depend on their metabolic activity for their primary function;
(e) medical devices that contain cells or tissues and that are the subject of investigational testing involving human subjects under Part 3 of the Medical Devices Regulations;
(f) cells, tissues and organs that are the subject of clinical trials under Division 5 of Part C of the Food and Drug Regulations;
(g) Class IV medical devices that are regulated under the Medical Devices Regulations;
(h) blood components, blood products and whole blood, except for cord blood and peripheral blood for use in lymphohematopoietic cell transplantation;
(i) cells and tissues that are regulated under the Assisted Human Reproduction Act or any of its Regulations; and
(j) semen that is regulated under the Processing and Distribution of Semen for Assisted Conception Regulations.

Non-application — Regulations

(2) No other regulation made under the Act applies to cells, tissues or organs that are the subject of these Regulations.

All CTO intended for transplantation are regulated pursuant to the F&DA, which provides the authority for developing regulations that are specific for different types of products. Although all CTO currently used for transplantation have an inherent infectious disease risk, they vary significantly with respect to other criteria. Consequently, CTO are subject to different regulations developed under the F&DA.

In general, cells and tissues are excluded from the CTO Regulations if they meet any of the following criteria:

a) they are more than minimally manipulated;
b) they are intended for non-homologous use (i.e., they are not intended to perform the same function in the recipient as they did in the donor or there is insufficient evidence to prove that the intended function is a native characteristic of the CTO);
c) they have a systemic effect and depend on their metabolic activity for their primary function, except for lymphohematopoietic cells that are derived from bone marrow, peripheral blood or cord blood and islet cells;
d) they are combined with non-tissue products such as artificial elements used for tissue engineering;
e) they are used in investigational studies involving humans, in order to establish their safety and effectiveness prior to being used in routine clinical practice (e.g., some emerging cell or gene therapy products have not been used in the clinical setting for sufficient time and in sufficient quantity to establish their safety and effectiveness for the intended use);
f) they are currently regulated as drugs or devices under other regulations.

It is important to note that even though autologous cells and tissues are excluded from the scope of the CTO Regulations, autologous and allogeneic cells and tissues that meet the criteria specified above in letters a) through f) that are for transplantation or assisted reproduction may nonetheless be subject to federal acts such as the F&DA and the Assisted Human Reproduction Act and their regulations.

In contrast to organs and minimally manipulated cells and tissues, more than minimal manipulation of cells and tissues may involve the addition of a wide variety of substances or the removal of biological components during processing. This could potentially alter their safety as well as the original or biological characteristics that are relevant for their claimed utility. Thus, clinical trials or investigational testing involving humans may be required to assess their safety and effectiveness.

With respect to cells and tissues that are proposed to be used in a manner that is not generally accepted to be a homologous use, sponsors will be required to provide evidence to support a claim of homologous use. Health Canada has the authority to require information regarding any relevant characteristics that must be maintained in order for a product to be considered homologous when distributed for a particular indication. This may include evidence to support the maintenance of these characteristics and their contribution to any product claims. Evidence to support that the product can effectively perform the proposed function in a safe manner may also be required.

As noted above, cells and tissues are excluded from the scope of the CTO Regulations if they have a systemic effect and depend on their metabolic activity for their primary function. When applied to cells and tissues, a systemic function can be interpreted as "a consequence or effect that is either of a generalized nature or that occurs at a site distant or not related to the location of the cell or tissue". An example of this situation is the transplantation of cells that are capable of producing and secreting hormones that act on diverse cells throughout the body. In general, these cells depend on their metabolic activity (e.g., the production of hormones and other substances) for their primary function.

Although cells and tissues that have a systemic effect are excluded from the CTO Regulations, some cells that meet this criterion have been exempted from this exclusion. Consequently, islet cells, and lymphohematopoietic cells that are derived from bone marrow, peripheral blood and cord blood, are subject to the CTO Regulations, even though they have a systemic effect and depend on their metabolic activity for their primary function. The exemption of these cells from the exclusion is based on the fact that their safety and effectiveness have already been demonstrated through clinical trials and/or established practice.

Islet cells and lymphohematopoietic cells that are derived from bone marrow, peripheral blood and cord blood, will only be subject to the CTO Regulations if they are minimally manipulated, i.e., if their processing only involves procedures used for pancreas digestion and for the purification of specific cell populations from a mixture of cells. Notwithstanding this exclusion, establishments must fully characterize these products, and evaluate their cell preparations to ensure they meet specifications set for cell number, identity, purity, viability, potency, etc. It should also be noted that if these cells are subject to procedures that are considered more than minimal manipulation (e.g., they are subject to ex-vivo expansion, cell differentiation, genetic manipulation, etc.), they will be subject to other regulations, including the Food and Drugs Regulations (F&DR) and/or the Medical Devices Regulations (MDR).

Demineralised bone that is combined only with a sterilizing, preserving or storage agent is considered minimally manipulated and would be considered a CTO; demineralised bone that is combined with a component other than a sterilizing, preserving or storage agent, is not considered a CTO but is regulated as a medical device. The addition of a handling component such as calcium carbonate or gelatin, used to modify the structure of the body, results in the product being regulated as a medical device under the MDR.

For questions regarding the classification of a CTO, you can contact the Biologics and Genetic Therapies Directorate of Health Canada at hc.bgtd.opic-bpci.dpbtg.sc@canada.ca.

## Prohibition (Section 4 of the CTO Regulations)

Transplantation

**4.** (1) Subject to sections 40 to 42, no establishment shall transplant a cell, tissue or organ unless it is processed by a registered establishment under these Regulations and determined safe for transplantation.

Importation — cells and tissue

(2) Subject to sections 40 to 42, no establishment shall import tissue or a cell, other than a lymphohematopoietic cell, unless it is processed by a registered establishment under these Regulations and determined safe for transplantation.

Importation — organs and lymphohematopoietic cells

(3) An establishment may import an organ or lymphohematopoietic cells from an establishment that is not registered.

With respect to imported tissue, evidence of the source establishment's Health Canada registration must be included on the exterior label. See section 31 for further guidance regarding the labelling of tissues. The importer must have a system in place to verify that the products have been processed by a registered source establishment and that they have been declared safe for transplantation. This should be done before importation from a new source establishment and periodically assessed to ensure that the source establishment continues to meet these requirements.

The term importation refers to the importation of CTO from outside Canada. Health Canada does not consider the shipment of CTO between different provinces or territories as importation.

## Registration (Sections 5 to 14 of the CTO Regulations)

Requirement to register

**5.** (1) Every establishment must be registered under these Regulations, except a retrieval establishment and, subject to subsection (2), a transplant establishment.

Exception

(2) A transplant establishment that distributes cells, tissues or organs must be registered under these Regulations.

Establishments that must register with Health Canada include the following:

- Canadian establishments responsible for processing organs from deceased donors
- Canadian establishments that transplant organs from living donors
- establishments responsible for the processing of tissues (live and deceased donors)
- Canadian establishments that transplant unbanked lymphohematopoietic cells
- Canadian establishments that process and store banked lymphohematopoietic cells
- establishments that distribute CTO within Canada to establishments outside their local health authority
- establishments that import CTO for distribution to establishments within Canada, including those within their own local health authority
- establishments responsible for the processing of islet cells
- establishments responsible for banking adjunct vessels that are not used immediately during transplantation of the donor organ with which they were retrieved.

Establishments that are not required to register with Health Canada include the following:

- establishments that only retrieve CTO
- establishments that only transplant banked lymphohematopoietic cells
- establishments that only transplant organs from deceased donors
- establishments that only transplant tissues
- foreign establishments that distribute either organs or lymphohematopoietic cells to Canada as per section 4(3)

- foreign establishments that only store or distribute CTO to Canada which they have received from a registered source establishment

Application
6. (1) An application for registration of an establishment must be made in the form established by the Minister, be dated and signed by the medical director or scientific director, and contain all of the following information:
  (a) the establishment's name and civic address, and its postal address if different, and the name and telephone number of a person to contact for further information with respect to the application;
  (b) in the case of an establishment that previously carried out its activities under another name, that other name;
  (c) a description of the types of cells, tissues and organs that the establishment processes, distributes or imports;
  (d) a description of the types of processing, distribution or transplantation activities that the establishment carries out or for which it is responsible;
  (e) the period during which the establishment has been in operation; and
  (f) a statement dated and signed by the medical director or scientific director that certifies that the establishment is in compliance with these Regulations.

Information on request
(2) An establishment must provide the Minister, on written request, with any relevant information necessary to complete the application, by the date specified in the Minister's request.

The CTO registration requirements:
- provide Health Canada with information regarding:
  a) the identity of the establishments, and programs that reside within establishments;
  b) the types of products being processed, distributed or transplanted and the types of activities being carried out;
  c) in the case of importers, the identity of the source establishment of the CTO
- require registrants to provide assurance to Health Canada that they have met the regulatory requirements with respect to organs and minimally manipulated cells and tissues they import, process, or distribute in Canada.

Section 6 of the CTO Regulations states the information that is required to be provided by an establishment in its application for registration form. All information requested under these Regulations is mandatory and must be included on the application form.

Establishments dealing with distinct programs (e.g. separate live donor and deceased donor programs; separate transplantation programs for youth and adults; separate programs with specialization in different types of CTO; or parent establishments of facilities that perform separate functions such as facilitating donor programs and operating a tissue bank) may benefit by submitting a different application form for each distinct program, as this would ensure the continuity of other services in the event that one program experiences complications; however separate applications are not required.

## Part 1: Type of application

Part 1 of the application form must include the type of registration. If this is the first time an establishment is applying for a registration number, then the establishment must indicate: "Initial Registration". For renewal applications, ensure that the correct box is selected and that when the renewal includes changes, the changes are clearly identified.

If the application is to register a change of information, the establishment must indicate: "Change of Information" and include its Health Canada registration number. If the application is a response to a renewal notice, the establishment must indicate: "Registration Renewal" and include its Health Canada registration number. In all cases the establishment must also indicate the date it began or will begin activities related to this registration.

## Part 2: Establishment Information

The full civic address of the establishment, including the postal or zip code and the mailing address if it is different from the civic address, must be entered. The contact information for the person responsible for the establishment is also required. It is essential that the establishment information and the contact information be accurate and complete, so as to ensure that Health Canada is able to communicate with the establishment. **This information must be kept up to date and is to be submitted as a change of information application within 30 days of making the change.**

If the establishment previously carried out its activities under another name, the previous name must be entered in the application form.

Establishments may include the program with their establishment name when the organization is very large and specialized. For example, Hospital X- Kidney Transplant Program. Note that the program name will appear on the CTO Registration certificate.

If the establishment has multiple addresses that do not function independently and are part of the same Quality Management System, complete the Establishment additional address section. Additional addresses do not hold the responsibility or liability for all CTO activities. The quality assurance activities are performed at a main establishment. For example, the determination of safety for transplantation of all CTOs would be done by the medical director and at the address of the main establishment.

The full civic address of the establishment's additional address and a description of activities at this address must be entered. The first additional address can be added into the form; for two or more addresses, a separate Annex 1can be completed for each additional address.

Date of start of activities (yyyy-mm-dd) is required for new applications only.

## Part 3: Type of Establishment

Part 3 of the registration application form requires the applicant to identify whether the establishment is a source establishment and a Canadian Importer or a Canadian Distributor.

If the application is for a source establishment, refer to Part 4 for further instructions.

A Canadian importer has their establishment civic address in Canada and obtains CTOs from outside of Canada for distribution to establishments within Canada, including those within their own local health authority. If the application is for an importer, refer to Part 4 for further instructions.

A Canadian distributor has their establishment civic address in Canada and distributes CTOs within Canada to establishments outside their local health authority. If the application is for a distributor, refer to Part 4 for further instructions.

## Part 4: Establishment activities and CTO information

Parts 4, 4A and 4B of the registration application form requires the applicant to provide details regarding the types of CTO being processed, imported and/or distributed by an establishment, and the types of activities it carries out. Foreign establishments that export to Canada should only list the products exported to Canadian establishments as well as the corresponding activities.

Part 4 is in a table format and the selections are indicated by clicking on the relevant boxes or by entering text where necessary.

The information in Part 4A is provided for activities (processing, importation or distribution) concerning deceased or living donors of organs and islet cells. The organs are listed on the left side of the table. The rows entitled "Other" are provided for the entry of any organ or islet cell not listed in the table.

Source Establishment
For source establishments, applicants should select the processing and the distribution activities for the specific products. If your establishment is also performing the activity of importation, importation should also be selected. An example is shown for a source establishment who processes kidney from deceased donors is shown below:

**Part 4: Establishment activities and CTO information**
(Check all activities and products that apply to your establishment)

**A) Organs and islet cells**

| - | **Activities** | | |
|---|---|---|---|
| | **Processing** (see definition in part 3) | **Importation** (into Canada) | **Distribution** (in Canada) |
| **Deceased donor** | | | |
| 1. Heart | ☐ | ☐ | ☐ |
| 2. Kidney | ☒ | ☐ | ☒ |

Part 4B provides space to include the activities (processing, importation or distribution and storage) concerning deceased or living donors of tissues including ocular tissues. The proprietary name and a description of the product should also be entered in this table as shown in the example below:

**B) Tissues , including ocular tissues**

| **Deceased donor** | | | | | |
|---|---|---|---|---|---|
| - | **Proprietary name and description** (if applicable) | **Processing** (see definition in part 3) | **Importation** (into Canada) | **Distribution** (in Canada) | **Storage** (Only applies to distributors/ importers) |
| 1. Bone | - | ☐ | ☐ | ☐ | ☐ |
| 2. Cartilage | - | ☐ | ☐ | ☐ | ☐ |

| | | | | | |
|---|---|---|---|---|---|
| 3. Tendon | - | ☐ | ☐ | ☐ | ☐ |
| 4. Skin | Product X - dermis | ☒ | ☐ | ☒ | ☐ |

The rows entitled "Other" are provided for the entry of any tissue or ocular tissue not listed in the table.

Establishments must identify each activity for which they are responsible, including the ones that are performed on their behalf by another establishment. Establishments that are performing activities for another do not have to check these activities on their registration form.

Importer
In case of an importer, you should select the importation, distribution and storage (if applicable) activities for the specific products. For example,

| **B) Tissues , including ocular tissues (Cont.)** | | | | | |
|---|---|---|---|---|---|
| **Living donor** | | | | | |
| | **Proprietary name and description** (if applicable) | **Processing** (see definition in part 3) | **Importation** (into Canada) | **Distribution** (in Canada) | **Storage** (Only applies to distributors and importers) |
| 1.Bone | - | ☐ | ☐ | ☐ | ☐ |
| 2. Skin | - | ☐ | ☐ | ☐ | ☐ |
| 3. Amniotic | Product Y - Amniotic Membrane | ☐ | ☒ | ☒ | ☒ |

As an applicant, if you are unsure of the classification of a product, please contact: hc.bpcp-pcpb.sc@canada.ca.

Should the applicant be unsure of which category the activities performed by their establishment falls into, a limited space is provided in Part 4D to include a description. This additional information should not include the submission of a detailed description of all the activities as previously listed in Part 4, but only the details that may be needed to clarify the information provided in Part 4 or to identify an activity not listed in Part 4.

The information in Part 4D should be limited to a description of the **types** of processing, distribution or transplantation **activities** that the establishment carries out if this information was not already provided in Part 4. **Details of the safety and efficacy of the products are not required for registration and should not be submitted**. It is recommended that the applicant hold onto such information until it is requested, and provide only a note in Part 4D that it is available if needed.

Distributor

In case of a distributor, the applicant should select the distribution and storage (if applicable) activities for the specific products. For example,

| **A) Tissues , including ocular tissues** | | | | | |
|---|---|---|---|---|---|
| **Deceased donor** | | | | | |
| | **Proprietary name and description** (if applicable) | **Processing** (see definition in part 3) | **Importation** (into Canada) | **Distribution** (in Canada) | **Storage** (Only applies to distributors/ importers) |
| 1. Bone | - | ☐ | ☐ | ☐ | ☐ |
| 2. Cartilage | - | ☐ | ☐ | ☐ | ☐ |
| 3. Tendon | - | ☐ | ☐ | ☐ | ☐ |
| 4. Skin | - | ☐ | ☐ | ☐ | ☐ |
| 5. Fascia | - | ☐ | ☐ | ☐ | ☐ |
| 6. Veins | Product Z – femoral vein | ☐ | ☐ | ☒ | ☒ |

## Part 5: Source establishment information

Canadian importers and Canadian distributors must identify the name of the source establishments, the CTO registration number and the type of CTO being imported or distributed.

**Part 5: Source establishment information**
**For Canadian importers and distributors only**

⚠

| Name of source establishment processing CTOs | CTO registration number | CTO type |
|---|---|---|

## Part 6: Other entity information and Annex 2 (if applicable)

Source establishments are required to complete Part 6. In some cases activities may not be performed at, or by, the establishment. As per subsection 6(d) of the CTO Regulations, an establishment must indicate the activities for which it is responsible. Part 6 requires the establishment to indicate another entity that performs activities on its behalf, whether under contract or not. If more than one other entity is needed, then a separate Annex 2 must be completed for each additional other entity. This part of the application should be duplicated as many times as is required in order to provide enough space to list information for all relevant establishments.

## Part 6: Other entity information
## For source establishments only

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If you need to list more than one other entity, please follow these steps:

1) Complete a separate "Annex 2: Other entity information" for each additional other entity.
2) Check the box below and indicate the total number of additional annexes for this section.
3) Attach the additional annex(es) to your submission.

☐ **Additional Annex 2 attached to this submission. Total number of Annex 2:_____.**

Other entity refers to an establishment that performs regulated activities such as transmissible disease testing or donor screening. For example if an organ donation organization (ODO) does the donor screening on behalf of a tissue bank then the ODO should be listed as an "other entity'. However, a tissue bank need not list each hospital, funeral home or hospice from whom ocular tissue is retrieved.

## Part 7: Statement of Compliance

The declaration section of the application contains the statement: "I hereby certify that the establishment named in this application is in compliance with the Safety of Human Cells, Tissues and Organs for Transplantation Regulations."

The medical director or scientific director must sign and date the declaration in order for the application to be processed. It should not be signed by the CEO, unless the CEO is also the scientific or the medical director. This authority can be delegated to another individual if this delegation of authority is clearly expressed in the establishment's Standard Operating Procedures (SOP). In signing the declaration, the signatory is attesting to the compliance of the establishment with the CTO Regulations. Making false, misleading, inaccurate or incomplete statements is grounds for refusal to issue a registration number, as per section 8 of the CTO Regulations.

The declaration of compliance signed by a medical or scientific director assures Health Canada that the establishment acknowledges its responsibilities under the CTO Regulations. This provides a level of assurance that CTO imported, processed, and/or distributed in Canada meet the safety requirements set out in the CTO Regulations, and that procedures are in place to protect the public should a problem be identified. This declaration of compliance does not preclude Health Canada from conducting inspections verifying compliance with the CTO Regulations.

All completed applications should be sent to the following email address: hc.rorb.cto-dgorr.sc@canada.ca.

Inquiries pertaining to the status of an establishment's registration can be directed to the following email address: hc.rorb.cto-dgorr.sc@canada.ca.

All other inquiries can be directed to: hc.bgtd.opic-bpci.dpbtg.sc@canada.ca.

Registration number
7. (1) On review of an application for registration, if the Minister determines that the information provided in the application is complete, the Minister must register the establishment and issue a registration number.
Validity
(2) Subject to section 9, a registration is valid until December 31 in the year after the year in which the registration number is issued.

All CTO Registration numbers expire on **December 31 of the year following the year in which it was issued.** For example:

- All certificates of registration issued in January 2018 will expire on December 31st, 2019.
- All certificates of registration issued in December 2018 will expire on December 31st 2019.

Notice of the requirement to complete an application for renewal will be provided by the Biological Product Compliance Program of Health Canada prior to the expiry date of the issued certificate of registration. When submitting an application, the establishment must ensure all relevant changes are appropriately referenced. Should an establishment not receive a notification of renewal, it should contact the Biological Product Compliance Program prior to the expiry date of its registration number: hc.rorb.cto-dgorr.sc@canada.ca.

Refusal
8. The Minister may refuse to register an establishment if he or she has reason to believe that any of the information provided by the establishment in its application is false, misleading, inaccurate or incomplete.

If issuance of a registration number is refused due to the conditions listed in section 8 of the CTO Regulations, the applicant will be notified and given an opportunity to be heard.

When registration may be cancelled
9. The Minister may cancel a registration in the following circumstances:
(a) the application for registration contains false or misleading information;
(b) the Minister receives a notice under section 13 that states that the establishment has ceased an activity;
(c) the establishment has not complied with a request for additional information made under section 14; or
(d) the Minister has reason to believe that the establishment is not in compliance with these Regulations or that the safety of cells, tissues or organs has been or could be compromised.

Actions before cancellation

**10.** (1) The Minister must take all of the following actions before cancelling a registration:

(a) send a written notice to the establishment that sets out the reasons for the proposed cancellation and specifies the corrective action, if any, that the establishment must take and the time within which it must be taken; and

(b) give the establishment an opportunity to be heard in writing with respect to the cancellation.

Notice of cancellation

(2) If the establishment does not carry out the corrective action to the Minister's satisfaction, or does not carry it out within the required time, the Minister must send a notice of cancellation of the registration that includes the reasons for the cancellation and the effective date.

Action by establishment when registration cancelled

**11.** On the cancellation of its registration, the establishment must immediately take both of the following steps:

(a) cease carrying out the activities that were authorized by the registration; and

(b) notify the establishments to whom it has distributed a cell, tissue or organ or made a donor referral, during the period specified in the notice, of the cancellation, the reasons for the cancellation and the effective date.

Cancellation in urgent circumstances

**12.** (1) Despite section 10, the Minister may cancel a registration immediately if he or she considers it necessary to do so in order to prevent injury to the health or safety of the public, by giving the establishment a notice of the cancellation in writing that states the reasons for the cancellation.

Request to reconsider

(2) An establishment may, in writing, request the Minister to reconsider the cancellation.

Opportunity to be heard

(3) The Minister must, within 45 days after receiving a request for reconsideration, provide the establishment with an opportunity to be heard in writing with respect to the cancellation.

Ongoing requirement to notify Minister

**13.** (1) Subject to subsection (2), an establishment must notify the Minister in writing of any change in the information provided in its application for registration, within 30 days after the change is made.

Cessation of activity

(2) If an establishment ceases to process, distribute or import cells, tissues or organs, it must notify the Minister in writing of that fact, within 90 days after it ceases that activity.

Contents of notice

(3) The notice must be dated and signed by the medical director or scientific director and include all of the following information:

(a) the establishment's name and civic address, and its postal address if different;

(b) the establishment's registration number;

(c) the date on which the change or cessation became effective; and

(d) in the case of the cessation of an activity, the disposition of the cells, tissues and organs in the establishment's possession.

The notification of changes identified under section 13 of the CTO Regulations should be sent to the Biological Product Compliance Program of Health Canada at the address specified in the guidance under section 6 of this document. It is recommended that establishments use the Human Cells, Tissues and Organs (CTO) for Transplantation Registration Application Form (FRM-0171) provided on the Health Canada Web site for this process. This includes change of contact information or change of address.

Establishments may submit changes electronically to the following email account: hc.rorb.cto-dgorr.sc@canada.ca.

The notice must be signed and dated by the medical or scientific director (or their designate) and include all of the information stated under subsection 13(3).

Additional information

**14.** An establishment must provide the Minister, on written request, with any additional relevant information to demonstrate that the activities it carries out are in compliance with these Regulations, by the date specified in the Minister's request.

Section 14 of the CTO Regulations can be applied in order to require an establishment to provide any relevant information that is required by Health Canada to determine whether the establishment is in compliance with the CTO Regulations.

## Source Establishment (Section 15 of the CTO Regulations)

Responsibility

**15.** A source establishment is responsible for the processing of cells, tissues and organs, whether the processing is carried out by the source establishment itself or by another establishment, and for determining whether the cells, tissues and organs are safe for transplantation.

The source establishment is responsible for the processing of CTO and for determining the CTO safe for transplantation. A source establishment is ultimately responsible for determining the safety of the CTO for transplantation, even if some or all of the processing activities were carried out by another establishment on behalf of the source establishment.

The determination of the source establishment in a given situation depends on the CTO in question, not the donor of the CTO, or the establishment of origin or facility where the donor was identified. Source establishment refers to the source of the CTO that has undergone all processing and is determined safe for transplantation.

For organs from a deceased donor, the organ donation organization (ODO) is the source establishment responsible for processing the organs. This reflects current practice in that the ODO will typically carry out the screening and testing of the donor, or donor suitability assessment, a pivotal component in determining whether or not an organ is safe for transplantation.

When an organ is retrieved from a deceased donor, it is common practice to simultaneously retrieve blood vessels from that donor, for the prospect of aiding organ transplantation. Under the CTO Regulations, these vessels are referred to as adjunct vessels and they are subject to the same regulatory requirements as organs.

In the event that the adjunct vessels are not used immediately in the transplantation of the organ with which they were retrieved, the establishment that takes responsibility for the storage and subsequent distribution of the adjunct vessels must register as a source establishment. Under these circumstances, the source establishment is responsible for ensuring that appropriate storage and documentation is provided for these vessels, if the vessels are stored with the intent of being subsequently transplanted. The source establishment is also responsible for ensuring that the vessels are used within a scientifically based predetermined number of days and for recording which establishment vessels have been distributed to. If the vessels are used within the source establishment, information that is capable of identifying the recipient must also be recorded. The adjunct vessels continue to be regulated as organs under the CTO Regulations and are not regulated as tissues. The source establishment must treat the vessels as if they were organs and is responsible for receiving and reviewing the relevant organ donor suitability assessment information, including the questionnaire, test results and the physical exam results, prior to transplantation, which is especially important in cases where the vessels are transplanted in an individual other than the original organ recipient.

Health Canada recommends that organ transplant establishments keep records of any adjunct vessels that are stored for future use, regardless of whether the transplant establishment is registered as the source establishment for the stored vessels or whether this responsibility is transferred to another party, such as an affiliated tissue bank. Furthermore, Health Canada recommends that organ transplant establishments inform source establishments if / where they store adjunct vessels that are not used during the surgical procedure of the organ recipient. This will help ensure that adjunct vessels can be appropriately identified and either quarantined or traced to a recipient in the event that any adverse reactions are reported in organ recipients that received an organ from the donor of the adjunct vessels.

Health Canada recognizes that, in some cases, adjunct vessels will need to be released prior to the source establishment's review of the documentation. Under these conditions, the transplanting physician may authorize the exceptional distribution of these vessels, if appropriate, under sections 40-42 of the CTO Regulations. In the case where exceptional distribution is applied to an organ of a donor, the exceptional distribution process does not have to be repeated for the use of the adjunct vessels retrieved from that same donor if the recipient of the organ and the vessels is the same person, and if the reason for the exceptional distribution is the same. The documentation requirements of sections 40-42 of the CTO Regulations must however be fulfilled.

For organ donation from a living donor, the source establishment responsible for processing of the organ is the relevant transplant establishment, which will need to register. The same is true for allogeneic (for use in another individual) lymphohematopoietic cell donations that are not banked. The transplant establishment continues to be the responsible source establishment regardless of which establishment carries out the assessment of the donor or which organization facilitates the matching of the donor and the recipient. For example, in the case of living donor kidney transplants that involve a donor who travels from the program where the donor workup and testing occurred or that involve an organ that is shipped for transplantation, the transplant establishment is still considered the source establishment. As such, the transplant establishment is responsible for obtaining and reviewing the appropriate documentation and determining the safety of the organ. The transplant establishment does not, however, need to repeat all of the donor screening and testing if it considers the existing results acceptable.

Health Canada recommends that the living donor organ donation and transplantation community work together to develop standardized SOP's and questionnaires to help ensure consistency with respect to donor screening and testing practices amongst the different organizations involved.

It is recognized that for unrelated lymphohematopoietic cell donations, the different activities carried out by the establishments involved may be on a continuum, in this case the source establishment is the transplant establishment, which will need to register. For example, even if the donor testing is initiated by a stem cell registry or a retrieval establishment the transplant establishment is responsible for reviewing these results and determining the safety of the donation.

For all tissues and lymphohematopoietic cells that are banked, the tissue or cell bank is the source establishment responsible for the processing and safety of the cells and tissues. This bank may be either a specific or a comprehensive tissue or cell bank. It should be noted that the term "banked" in this context does not refer to cells and tissues that are obtained from a source establishment and stored by the end user for a period of time before use in transplantation. Under the CTO Regulations, "banked" cells and tissues are those that have been determined to be safe for transplantation, are stored by the **source establishment** in their inventory and are available for distribution and transplantation. In the case of lymphohematopoietic cells collected from bone marrow or peripheral blood, any storage of the cells is not considered banking if the donation is reserved for the treatment of a designated recipient.

Here is an example to illustrate the definition of source establishment in the case of a multiple tissue/organ donor, where there may be more than one source establishment for a given donor. For example, a case where bone, ocular tissue, kidney and liver were to be retrieved from a donor:

As per the definition in the CTO Regulations, the ODO would be the source establishment responsible for the processing and safety of the organs, whereas the processing and safety of the bone and ocular tissue would be the responsibility of the bone and eye bank, respectively. Similarly, if the bone and ocular tissue were retrieved for a comprehensive tissue bank, then that tissue bank would be responsible for the processing and safety of the tissues.

It is important to note that, although an establishment is the source establishment in one circumstance for a particular CTO, it does not mean that the establishment will necessarily be the source establishment for all CTO that it handles or processes. A good example of this is an ODO. An ODO is the source establishment for organs from deceased donors, and while it may be involved in tissue donation, it is **not** the source establishment for tissue.

Each establishment must rely on the Regulations and the definitions contained within them aided by this guidance document in order to determine its responsibilities for the safety and processing of CTO under these Regulations. There should be an agreement among all establishments involved in processing the CTO with respect to determining which establishment will function as the source establishment.

It is important to note that composite tissues, which are vascularized composite allografts consisting of multiple tissue types (e.g., a full face or hand transplant), can meet the definition of a tissue or an organ under the CTO Regulations. It is up to the source establishment to determine which set of regulatory provisions is most appropriate for their circumstances. Provided that all of the most pertinent regulatory provisions relating to either tissues or organs are met, the composite tissue can be distributed (without using exceptional distribution) by an organ or tissue source establishment that is registered as per Section 5 of the CTO Regulations.

## Processing (Sections 16 to 27 of the CTO Regulations)

The extent of the responsibility of source establishments for the processing and safety of CTO under section 15 of the CTO Regulations is determined by the meaning of the term "processing". Processing as defined in section 1 of the CTO Regulations includes the following activities (see definitions for a more detailed description of each activity).

(a) donor screening;
(b) donor testing;
(c) donor suitability assessment;
(d) retrieval, except for organs and islet cells;
(e) testing and measurements performed on the cells, tissues or organs after they are retrieved;
(f) preparation for use in transplantation, except for organs;
(g) preservation;
(h) quarantine;
(i) banking; and
(j) packaging and labelling.

Each of these activities is described in more detail under the applicable regulatory requirements below. Information about donor suitability assessment, including donor screening and testing, is organized as follows:

- section 18 contains the general requirements for all CTO except lymphohematopoietic cells;
- sections 20, 21 and 22 contain additional requirements regarding tissues, ocular tissues and organs, respectively; and
- section 23 contains all the requirements for lymphohematopoietic cells.

The responsibility of source establishments for the activities described applies **whether or not the source establishment carries out the activities itself, or if they are performed by another establishment on behalf of the source establishment.**

Documented evidence

16. An establishment must have documented evidence that demonstrates that the activities, processes and technical procedures that it uses in processing cells, tissues and organs will consistently lead to the expected results.

In the context of these Regulations, documented evidence refers to activities, processes and technical procedures that have been validated by the establishment, or, as appropriate, that have been established in standards developed by recognized professional organizations, based on established practice, or that are supported by information available in the scientific literature.

When pooling permitted

17. An establishment may only pool cells, tissues or organs from different donors during processing to create a therapeutic dose for a single recipient.

Requirements — cell, tissue and organ donors

18. In assessing the suitability of a donor of cells, tissues or organs, except a donor of lymphohematopoietic cells, an establishment must perform all of the following steps:
    (a) obtain the donor information and history in accordance with sections 12.2 and 12.3 of the general standard;
    (b) determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.1.3 of the general standard and in Annex E to that standard;
    (c) perform a physical examination of the donor in accordance with section 13.2 of the general standard; and
    (d) perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.6 of the general standard.

Section 18 applies to all cells, tissues and organs with the exception of lymphohematopoietic cells. See section 23 for donor suitability requirements for lymphohematopoietic cells.

## Donor Suitability Assessment

Donor suitability assessment (section 12.2 of the general standard), which is intended to elicit risk factors, is generally based on a medical and social history, clinical status, physical examination, tests and if performed, an autopsy. Documentation of this assessment must include all the elements specified in section 12.3 of the general standard.

In cases where an autopsy is to be performed, and it is determined that the integrity of the CTO will be compromised before the report is completed, need not wait for the review of the final report of the autopsy results. Rather, it is recommended that the presumed cause of death and other pertinent preliminary autopsy findings would be taken into consideration and documented.

## Donor Screening

Donor screening is one component of donor suitability assessment and is intended to elicit general health information and identify risk factors (e.g., infectious disease risks) that could potentially impact the safety of the CTO. This risk assessment is based on the donor's medical and social history, clinical status, physical examination tests and if performed, an autopsy. The information regarding the donor's medical/social history and clinical status can be obtained through a donor interview and a review of the donor's medical records or charts. The interview shall be conducted using a medical/sexual/social history questionnaire that includes the applicable contraindications/exclusion criteria and other relevant questions required as per the CTO Regulations, and should be documented in the form of a checklist where the response/outcome for each criterion is recorded. If the donor is deceased or is unable to participate in the interview, the interview may be carried out with one or more individuals who can provide the necessary information, such as the donor's next of kin or nearest available relative, an individual with a relationship with the donor (e.g., caretaker, friend, partner), a member of the donor's household, or the donor's primary physician. It is recommended that the interview take place in person or by telephone.

An establishment must develop and maintain SOPs for all steps performed during donor screening, including those governing the conduct of the donor medical/sexual/social history interview and the administration of a donor screening questionnaire(s). If a questionnaire developed by a professional organization is to be used, an establishment must review the questionnaire to determine if it meets all the requirements of the CTO Regulations for donor screening.

It is recommended that living donor screening be performed as close to the time of retrieval as feasible. In the event that more than one month has elapsed since the donor screening questionnaire was completed and the retrieval has not yet occurred, Health Canada recommends reviewing the living donor screening results with the donor as close to the time of retrieval as feasible in order to ascertain whether any of the information has changed. In such instances an abbreviated donor screening questionnaire would be acceptable provided it addresses all the necessary exclusion criteria.

When a potential donor is part of the Medical Assistance in Dying (MAID) program, the information communicated by the living potential donor may be considered part of the donor screening assessment, provided there is verification that the information continues to be true within the necessary timeframes for donation and the assessment is completed in accordance with the establishment's SOP.

With respect to donor screening for donors less than 11 years of age, the screening questions used to determine high risk for HIV, HBV or HCV shall be collected in a manner that is appropriate to the age of the donor as described in the establishment's SOP.

## Contraindications/Exclusion Criteria

The conditions and behaviours set out in section 13.1.3 and Annex E of the general standard may increase the risk that a donor may have and/or could potentially transmit an infectious disease to the recipient. For this reason, donors shall be excluded from donating CTO on the basis of these contraindications/exclusion criteria, except in cases where exceptional distribution is used (see sections 40 to 42 of the CTO Regulations for more information).

Examples of prion related disease that are described as exclusion criteria in section 13.1.3 of the general standard include, but are not limited to, Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease and other transmissible spongiform encephalopathies.

Examples of degenerative neurologic disorders of viral or unknown etiology that are described in section 13.1.3 of the general standard include, but are not limited to, Parkinson's disease, subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy and amyotrophic lateral sclerosis or Lou Gehrig's disease.

Section 13.1.3 of the CSA General Standard states the following:
A donor shall be excluded if any of the following contraindications apply:

i) persons with a history of infection with HIV, clinically active HCV, or clinically active HBV;

This clause has been amended to refer to persons with a history of clinically active HBV or HCV. The purpose of this amendment is to clarify that in cases where there was a suspicion of hepatitis in the donor's medical history, outside of the current donor suitability assessment, that it may be possible to requalify the donor if the validity of this historical information is in question. This can be accomplished by performing the necessary donor screening and testing required under the CTO Regulations. In addition, it is recommended to perform NAT under these circumstances as a precautionary measure.

Section 13.1.3 (f) of the general standard excludes donors "with active encephalitis or meningitis of infectious or unknown etiology". Undiagnosed meningitis or encephalitis has been associated with high rates of transmission of infection to organ recipients. These central nervous system infections can lead to significant morbidity and mortality. The Organ Procurement and Transplantation Network, together with the United Network for Organ Sharing, has developed a guidance document detailing the Ad Hoc Disease Transmission Advisory Committee's (DTAC) practical guidance on the evaluation of potential organ donors for meningoencephalitis during the donor screening process. This guidance document could serve as a useful resource for ODOs as well as transplant programs.

In addition, other infections may exclude the donation of a CTO, if the infection would pose a significant risk to the recipient if transmitted.

## Physical Examination

Prior to the donation of CTO (with the exception of lymphohematopoietic cells, which are dealt with under section 23) from a potential donor, a physical examination must be performed by a qualified person in accordance with the establishment's SOP (in accordance with section 13.2 of the general standard).

When a potential donor is part of the Medical Assistance in Dying (MAID) program, a physical exam of the living potential donor may be considered part of the donor screening assessment, provided there is verification that the information continues to be true within the necessary timeframes for donation and the assessment is completed in accordance with the establishment's SOP. Any mandatory living donor tests, for which results are not obtained, must result in the organs being distributed under exceptional distribution only.

### Deceased Donors:

In the case of a deceased donor, the mandatory physical examination includes a recent antemortem or postmortem physical examination, a directed physical examination and may include a limited autopsy, if performed. The directed examination should include any of the applicable items included below that would assist in determining whether there is evidence of high risk behaviour.

Together, with information gathered as part of the donor medical/social history, the following physical evidence is used to evaluate the donor's risk of having a transmissible disease. Not all of the identified risk factors will necessarily lead to exclusion of the donor; however, the information gathered is expected to be important for clinical decision-making.

The following physical evidence are examples that may be associated with the presence of a transmissible disease and should be assessed in a directed physical examination performed on all potential deceased CTO donors:

- signs of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, syphilis, chancroid;
- for a male donor, physical evidence of anal intercourse including perianal condyloma;

- physical evidence of nonmedical percutaneous drug use such as needle tracks, including an examination of tattoos as they may cover needle tracks;
- physical evidence of tattooing, ear piercing, or body piercing;
- disseminated lymphadenopathy (swollen lymph nodes);
- oral thrush;
- blue or purple spots consistent with Kaposi's sarcoma;
- unexplained jaundice/icterus or hepatomegaly (hepatomegaly may not be apparent in a physical examination unless an autopsy is performed).
- physical evidence of sepsis, such as unexplained generalized rash;
- large scab consistent with recent smallpox immunization;
- eczema vaccinatum;
- generalized vesicular rash (generalized vaccinia);
- severely necrotic lesion consistent with vaccinia necrosum; and/or
- corneal scarring consistent with vaccinial keratitis.

Health Canada acknowledges that the probability of encountering signs of physical evidence associated with a recent smallpox (vaccinia) immunization is very remote; however, there does exist a possibility that one could encounter these signs in a small number of individuals such as those who perform laboratory work involving orthopoxviruses, military personnel who have served or will serve overseas, and first responders that are specially trained to respond to threats of bioterrorism.

The physical examination of skin donors shall include documentation of findings and conditions that may affect the quality or quantity of skin retrieved.

Living Donors:

In the case of a potential living donor, all donors must be given a physical exam which assesses for evidence of certain high risk behaviour (such as needle tracks or other signs of injection drug use), signs of bacterial, fungal, parasitic or viral infections of clinical significance and signs of malignancy.

Health Canada recommends that physical exams be performed as close to the time of retrieval as is reasonable and practical. Under normal circumstances, physical exams should be conducted within 30 days of the anticipated date of retrieval. If the retrieval of the organ or tissue is postponed, it will be left up to the clinical judgment of the source establishment to determine whether a repeat physical exam, or a limited repeat physical exam, is warranted.

If an examination of the donor was previously performed for other reasons, such as an assessment to determine if donation is safe for the donor, findings of such an examination can be reviewed and documented in the donor's records in lieu of a new physical examination, assuming the exam was performed within the recommended timeline. Since the findings of a physical exam performed for other reasons may not be reported in a manner that specifically addresses the risk factors of interest, a new physical exam must be performed to confirm or rule out **potential** risk factors that are identified during the medical/social history review. The new physical exam shall assess any physical evidence that could indicate high-risk behaviour associated with the presence of a transmissible disease.

With respect to the donation of amniotic membrane tissue, a surrogate physical examination of the mother must be performed and the results must be documented.

### Standard Operating Procedures (SOPs)

An establishment must have SOPs describing how to conduct physical examinations of donors.

## Donor Testing

## General Requirements

Donor testing may include, but is not limited to, laboratory tests for transmissible disease agents (e.g., HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV)); tests performed to determine the donor's blood type (i.e., ABO group and Rh type); or any procedures done to evaluate or provide information on the CTO itself. The guidance provided below for donor testing focuses on laboratory tests for the various transmissible disease agents applicable to CTO donors.

For information related to donors of lymphohematopoietic cells, refer to section 23 of the CTO Regulations.

## Time Frame for Specimen Collection

Ideally, specimens for infectious disease testing for all CTO donors should be collected as close to the donation as possible. Health Canada considers the maximum time frames in Table 1 to be appropriate and effective:

**Table 1**: Timeframe for Specimen Collection for HIV-1, HIV-2, HCV, and HBV Testing and any Additional Testing for Diseases or Disease Agents as Specified in the Infectious Disease Testing Requirements of the Applicable Subset Standards

| Type of CTO | Type of Testing Required | Timeframe |
|---|---|---|
| Tissue from deceased infant donor ≤ 28 days old and who had no obvious potential exposure to a blood born pathogen after birth | serological screening tests plus NAT for HIV-1 and HCV performed on birth mother . | within 7 days before or after time of death |
| Tissue from deceased infant donor > 28 days old* | serological screening tests plus NAT for HIV-1 and HCV performed on infant donor. | within 7 days before or after time of death |
| Tissue from deceased donor* | serological screening tests performed on donor plus NAT for HIV-1 and HCV. | within 7 days before or after time of death |
| Tissue from live donor | serological screening tests performed on donor | within 7 days prior to donation or up to six weeks following donation and again after 180 day quarantine (unless NAT also performed for HIV-1 and HCV) (exception for ocular tissue, within 7 days of donation) |
| deceased organ donor | serological diagnostic or screening tests performed on donor | As close to the time of donation as possible. The tests should be performed on the most recent sample for which donor identity and sample quality can be ensured. |

| | | |
|---|---|---|
| live organ donor (including MAID organ donors) | serological diagnostic or screening tests performed on donor | within 30 days before donation and it is recommended to retest at the time of donation |
| Organ from infant donor ≤ 28 days old | serological diagnostic or screening tests performed on birth mother | within 7 days before or at the time of donation |
| Organ from infant donor > 28 days old but < 18 months or who was breast fed in the last 12 months | serological diagnostic or screening tests performed on the infant donor as well as the birth mother, unless HIV-1 and HCV NAT is performed on the infant, in which case all tests need only be performed on the infant. | within 7 days before or at the time of donation |

*While antemortem or postmortem specimens are considered acceptable it is recommended that a pre-mortem specimen be used, if available. This may be preferable as it is likely to be less hemolyzed, and excessive hemolysis can interfere with the test results. In addition, the donor may have received fluid infusions shortly before dying, resulting in plasma dilution sufficient to affect test results

Note: NAT for HIV-1 and HCV is mandatory for tissue (including ocular tissue) from deceased donors but is not necessary for tissue from living donors if the 180 quarantine and donor retesting protocol is followed.

Establishments must have SOPs that specify the time frames for the collection of blood specimens from donors of each type of CTO.

### Infectious Disease Testing

All source establishments are responsible for infectious disease testing, including testing which is carried out on its behalf by another establishment. They must have appropriate documentation (e.g., SOPs, agreements, contracts, or audit reports) to support that infectious disease testing is performed in accordance with the following:

1) Testing shall be performed by a laboratory that meets applicable requirements of the authority having jurisdiction over that laboratory.
2) The tests for infectious diseases or disease agents that could lead to the exclusion of the donor (i.e., diseases or disease agents that are exclusion criteria under the CTO Regulations) must be performed using test kits that are licensed as required in sections 25 and 26 of the CTO Regulations. The tests for infectious diseases or disease agents that do not lead to donor exclusion, (e.g. CMV), must be performed using test kits that are licensed as required in section 25.
3) The testing laboratories must follow the test kit manufacturer's instructions with respect to the following:
    a. the collection, handling, and storage of blood specimen;
    b. the time frame within which samples must be tested, if applicable;
    c. the procedure for testing and
    d. the interpretation of the test results.

### Interpretation of Infectious Disease Test Results

The terms used by test kit manufacturers for the interpretation of serological test results are determined in part, by the testing algorithms used. In general, the initial serological screening test is performed using a single blood sample. A nonreactive sample is considered a negative test result and further testing is not required. In contrast, a reactive sample is considered initially reactive instead of positive because (1) the sample has to be retested in duplicate using the same test but not necessarily the same lot; and (2) the results are considered repeatedly reactive if either one of the two replicates is reactive. These two additional steps are necessary to achieve the final outcome (i.e. "positive" or "negative") of the test kit in the event that a sample is initially reactive. It is important to note that this testing algorithm is intended to serve only as an example and establishments must always apply the specific testing algorithm proposed by each test kit manufacturer.

It should also be noted that some test kit manufacturers may only consider a sample to be positive once confirmatory or supplemental testing with a different test kit is performed to confirm the results of the first test kit. While confirmatory testing is necessary for patient diagnosis, it should not be considered for the purpose of donor screening because false negative confirmatory test results cannot be ruled out. Thus, in these circumstances, donors must still be excluded regardless of the results of confirmatory tests.

Establishments that use third party testing labs must ensure that, in cases where confirmatory testing is performed for patient diagnosis, they are provided the results of the initial test kit in order to be able to make the appropriate determination of donor eligibility.

In addition, some test kit manufacturers do not use the term "repeatedly reactive" for the final outcome of a particular screening or diagnostic test. Instead, they use the terms "reactive" or "positive" for the final outcome of these tests.

In this guidance document:

1) A **negative** test result means the **final outcome** in which the test specimen is determine to be nonreactive by the test kit manufacturer.
2) A **positive** test result means the **final outcome** in which the test specimen is determined to be "reactive", "repeatedly reactive" or "positive" according to the testing algorithms proposed by the test kit manufacturer.
3) A **confirmed positive** test result means the outcome of a confirmatory or supplemental test performed using a **different test kit,** in which the tested specimen is determined to be reactive.

Donor eligibility determination shall include the interpretation of the infectious disease test results as outlined below:

1) For HIV-1 and 2, HBV, HCV and HTLV-I and II, CTO shall not be released for transplantation if the donor's specimen is positive for any of the infectious disease markers specified in this document. In cases where additional tests are performed to confirm or supplement the positive test results (e.g., for the purpose of donor or next-of-kin notification), CTO shall not be released for transplantation, unless the exceptional distribution provisions are met, even if the confirmatory or supplemental test results are negative.
2) For Syphilis, CTO may be released for transplantation if the donor's blood sample is positive using a nontreponemal test, but negative using a treponemal-specific confirmatory assay. It should be noted that if establishments decide to use a treponemal-specific assay for syphilis as the test of record, the CTO shall not be released for transplantation if the donor's specimen is positive unless the exceptional distribution provisions are met. This is because a positive treponemal-specific test identifies both recent syphilis infections, and remote or treated syphilis infections. While a nontreponemal test can be performed to rule out a recent infection, false negative results cannot be ruled out. Thus, appropriate testing algorithms need to be developed to resolve this issue.
3) For cytomegalovirus (CMV) and Epstein-Barr virus (EBV), the cells or organ may be released for distribution if a donor's blood sample is positive, or if the test results are pending. It is not necessary to use exceptional distribution under these circumstances. The test results for these infectious agents may be important in selecting the cells or organ for specific patients and can impact recipient monitoring protocols. These results must be communicated to the transplant physicians.
4) For toxoplasmosis tests for heart donors, the determination of donor eligibility is not based on the test results, and the tests may therefore be performed retrospectively. However, the test results are important for the monitoring of heart recipients and must be communicated to the transplant physicians when they become available. Note that positive results that are received post transplantation are not considered an

error/accident under the CTO regulations unless the test was initially reported as negative and then the results were determined to be positive.

5) If an establishment performs additional tests that are not mandatory (e.g., nucleic acid testing (NAT) for HIV-1, HCV, HBV and WNV for organ donors, etc.), or obtains such test results for a shared donor from another establishment, the results must be taken into consideration when determining donor eligibility if they are available prior to the release of CTO.

If a donor's specimen tests positive for HIV, HBV or HCV using a required serological test, but is found to be negative using NAT, the CTO cannot be distributed, unless done under exceptional distribution.

It should be noted that exceptional distribution may be used if the donor specimen is repeatedly reactive or positive for markers of infectious disease agents. More information on exceptional distribution can be found in sections 40 to 42 of the CTO Regulations.

Results of all tests, including those that are optional, must be included in the donor records. Establishments must have SOPs for the interpretation and handling of all test results, including the communication of test results to transplant physicians or to establishments to which the CTO are distributed. Procedures must also be established for handling the results of tests that become available after the CTO has been released for distribution, and must include notification of transplant physicians or establishments to which the CTO is distributed.

### Archived Samples

The CTO Regulations do not require the collection of samples for archiving as this has no impact on the safety of CTO that meet current regulatory requirements. It is however recommended that cell, tissue, plasma or serum samples from each donor be archived for retrospective testing of donors of cells and tissues that are still in inventory when new tests are adopted for screening donors for existing or emerging pathogens. The requirement for such retrospective testing will be based on the degree of safety enhancement afforded by the new tests, and the availability of tests that are appropriately validated or approved under the MDR for testing frozen specimens. If such retrospective testing is required, Health Canada will inform CTO establishments.

If establishments choose to archive samples, they must have SOPs for the collection and storage of samples for archiving. Samples must be stored frozen, and should be kept for at least 5 years. Establishments must have documentation to show that the samples are maintained at the appropriate temperature throughout the storage period.

## Tests that are considered appropriate and effective

### Mandatory Testing

All CTO donors must be tested for the infectious disease agents listed in the sections of the general standard referenced in the CTO Regulations, using appropriate and effective tests. A test is considered appropriate and effective if (i) it is licensed for the detection of the infectious disease agent or marker in accordance with the licensing requirements specified in sections 25 and 26 of the CTO Regulations; (ii) it is used in accordance with the test kit manufacturer's instructions; and (iii) it is used for the detection of an infectious disease marker that is relevant at the time testing is performed. A list of such appropriate infectious disease markers is provided below (see Appendix 2 also for a complete list of all required and recommended tests). This list may be revised when new infectious disease tests become licensed, or when new information necessitates an amendment.

Section 14.2.6.1 of the general standard specifies the infectious disease agents for which testing must be performed for all CTO donors, and requires that any additional tests specified in the subset standards be performed. The following sections provide a list of infectious disease markers that are considered appropriate and effective for the detection of donors infected with the disease agents listed in the general and subset standards. This list may be revised when new infectious disease tests become licensed, or when new information necessitates an amendment.

Health Canada considers tests for the following infectious diseases markers to be appropriate and effective in order to comply with section 14.2.6.1 of the general standard

a) antibodies to the human immunodeficiency virus, types 1 and type 2 (anti-HIV-1 and anti-HIV-2);
b) hepatitis B surface antigen (HBsAg);
c) total antibody to hepatitis B core antigen (anti-HBc, IgG and IgM);
d) antibodies to hepatitis C virus (anti-HCV).
e) nucleic acid testing (NAT) for the detection of HIV-1 in deceased tissue donors and ocular tissue donors
f) nucleic acid testing (NAT) for the detection of HCV in deceased tissue donors and ocular tissue donors

In the case of infant donors who are less than 18 months old, or who were breastfeeding at any time during the 12 months prior to donation, both the birth mother and the donor must be tested for infectious disease agents, in order to address vertical transmission of infectious agents from the birth mother to the donor (section 14.2.6.2 of the general standard). However, the following exceptions apply:

For donors who are 28 days old or younger and who had no obvious potential exposure to a blood born pathogen after birth, surrogate testing of the birth mother need only be performed.

For donors who are 29 days old or older, if nucleic acid testing is used for the detection of HIV-1 and HCV, all testing in 14.2.6.1 of the general standard need only be performed on the infant donor.
Establishments must have SOPs that describe which infectious disease tests must be performed, and when testing of the birth mother is required for infant donors.

## Recommended Testing

Living organ donors should also be tested for HIV-1 and HCV using NAT. In particular, NAT should be performed on organ donors (living and deceased) in circumstances where it is clinically indicated, for example, if a decision is made to use exceptional distribution for a CTO from a donor with a history of high risk behaviour and a negative serological test for HIV and HCV.

Organ donors, islet cell donors, and tissue donors (including ocular tissue donors) should be tested for WNV using a test kit that has been licensed for the detection of viral nucleic acid. Testing could be performed on a seasonal basis if specific procedures are in place to determine the time frames for seasonal testing and to determine other circumstances when testing for WNV may be required outside of these time frames, e.g., when a donor has travelled to an endemic area.

Given the transient nature of WNV viremia, Health Canada recommends that testing be performed on blood samples collected on the day of donation or as close to the time of donation as is feasible, taking into consideration WNV testing turnaround times. It is acknowledged that similar to other infectious diseases, donors could become infected with WNV after sample collection but before donation if the samples are collected prior to donation. This could be addressed through additional screening and/or testing of samples collected on the day of donation.

A test kit has been licensed by Health Canada for the detection of WNV ribonucleic acid in plasma specimens from both living and deceased donors.

The Medical Device Bureau of the Therapeutic Products Directorate is the Canadian federal regulator responsible for licensing in accordance with the F&DR and the MDR.

## Medical Devices Active Licence Listing (MDALL)

A database containing all licensed Class II, Class III and Class IV Medical Devices for sale in Canada can be found on the Health Canada Web site. On the Medical Devices Active Licence Listing (MDALL), "active licence search" page, the licensure of test kits approved for donor screening can be verified.

Plasma dilution algorithm

**19.** In assessing the suitability of a donor, an establishment must apply a plasma dilution algorithm if a donor pre-transfusion or pre-infusion blood sample is unavailable.

Blood transfusion or infusion of intravenous fluid could dilute the donor's blood and lead to a decrease in concentration of circulating antigens and antibodies. This could lead to false negative results for infectious disease tests.

**Testing must be performed on a suitable blood sample**, as defined by the establishment's SOPs that is collected as close to the time of retrieval as possible. It is recommended that testing be done on the **most recent pre-transfusion/infusion blood sample** for which identity and quality can be ensured. If no suitable pre-transfusion/infusion blood sample is available, benchmarks for **plasma dilution** shall be applied to determine whether the degree of plasma dilution is or is not sufficient to affect test results. If there is no suitable pre-transfusion/infusion blood sample available for testing and no other suitable specimen is available for testing based on the results of the plasma dilution algorithm, this constitutes a contraindication to donation.

Establishments must have SOPs that describe situations that could result in plasma dilution, as well as the collection of pre-transfusion/infusion samples.

Health Canada does not provide guidance with respect to the types of infused fluids to consider when calculating plasma dilution, nor do we recommend or review any specific plasma dilution algorithms. Establishments must develop their own Standard Operating Procedures that outline their plasma dilution algorithms. Establishments must use an algorithm that has been validated, established in standards developed by recognised professional organizations or that is supported by information available in the scientific literature.

Additional exclusion criteria — tissue donors

**20.** In assessing the suitability of a tissue donor, except an ocular tissue donor, an establishment must perform both of the following steps:
   (a) determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.1.2 of the tissue standard; and
   (b) perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.6 of the tissue standard.

## Contraindications/Exclusionary Criteria

In addition to the exclusion criteria of section 13.1.3 of the general standard, donors shall be excluded from donating tissues on the basis of the exclusionary criteria in section 13.1.2 of the tissue standard.

## Tests that are considered appropriate and effective

### Mandatory Testing

In addition to tests for the disease or disease agents specified in section 14.2.6 of the general standard, Health Canada considers the following tests to be appropriate and effective for testing tissue donors in order to comply with section 14.2.6 of the tissue standard:

a) serologic assays for the detection of antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and HTLV-II) for donors of viable, leukocyte-rich tissue; and

b) non-treponemal or treponemal-specific serologic assays for the detection of syphilis

Please refer to Table1 for timeframes for specimen collection. Note that Health Canada will permit exemptions from the requirement to perform NAT in the case of fresh tissue grafts that cannot be stored for a sufficient period of time to allow for the receipt of NAT results prior to transplantation. Establishments that wish to exempt fresh tissue grafts from NAT must ensure that the appropriate documentation exists in their SOP's to support such exemptions. SOP's must describe which tissues are exempt from NAT, the rationale for exemption, and any circumstances under which NAT is or is not to be used. In such cases, fresh tissue grafts can be distributed without having to use exceptional distribution when NAT is not performed.

Recommended Testing

Health Canada recommends that donors of tissues not considered leukocyte-rich also be tested for HTLV-I and HTLV-II.

Tissue that is not considered leukocyte-rich include, among others, bone, cartilage, corneas, ligaments, sclera, skin, tendons and amniotic tissue. Osteoarticular allograft tissue is not considered leukocyte rich.

## Other Eligibility

In addition, Health Canada has issued measures to address the potential risk of Zika virus transmission through human cells, tissues and organs. A notice containing the measures can be found in Appendix 3.

Additional exclusion criteria — ocular tissue donors

**21.** In assessing the suitability of an ocular tissue donor, an establishment must determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in sections 13.1.3 to 13.1.6 of the ocular standard.

## Contraindications/Exclusionary Criteria

In addition to the exclusion criteria of section 13.1.3 of the general standard, donors shall be excluded from donating ocular tissue on the basis of the exclusionary criteria in sections 13.1.3 to sections 13.1.6 of the ocular standard. Note that 13.1.3 (h) and (l) of the ocular standard are not intended to exclude the use of healthy tissue from a donor with intrinsic eye disease or a congenital or acquired disorder that only affects one eye. The contraindication is intended to only apply to the affected eye.

## Eligibility based on HTLV and syphilis testing

When testing for anti-HTLV-I or anti-HTLV-II has been performed on an ocular tissue donor (e.g., for the purposes of organ donation from the same donor) and any such tests are positive, ocular tissue may be used for transplantation without having to use exceptional distribution, subject to the approval of the source establishment's Medical Director.

When testing for syphilis has been performed on an ocular tissue donor (e.g., for the purposes of organ donation from the same donor) and any such tests are positive, ocular tissue may be used for transplantation without having to use exceptional distribution, subject to the approval of the source establishment's Medical Director.

## Other Eligibility

In addition, Health Canada has issued measures to address the potential risk of Zika virus transmission through human cells, tissues and organs. A notice containing the measures can be found in Appendix 3.

Additional requirements — organ and islet cell donors

**22.** (1) In assessing the suitability of an organ or islet cell donor, an establishment must perform all of the following steps:

- (a) obtain the donor information and history in accordance with sections 12.2.2.3, 12.2.2.4, 12.2.3.4 and 12.2.3.7 of the organ standard;
- (b) determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.2.2 of the organ standard;
- (c) perform the tests specified in sections 14.1.2 and 14.3.2 of the organ standard; and
- (d) perform appropriate and effective tests for the diseases or disease agents specified in sections 14.2.6.3 and 14.2.6.6 of the organ standard.

Exception — imported organs

(2) Despite subsection (1), in the case of an imported organ, the transplant establishment need only have the following:

- (a) documentation of the donor suitability assessment according to the requirements of the jurisdiction where the assessment was performed;
- (b) documentation that the tests specified in sections 14.1.2 and 14.3.2 of the organ standard have been performed;
- (c) documentation that appropriate and effective tests for the diseases or disease agents specified in sections 14.2.6.3 and 14.2.6.6 of the organ standard have been performed; and
- (d) in the case of those of the tests for the diseases or disease agents specified in section 14.2.6.3 of the organ standard that must be performed before transplantation and the blood group test for ABO, a copy of the test results.

## Donor information and history

Section 12.2.2.3 of the organ standard requires that any previous residence outside Canada and travel history in the past six months be documented for all donors. Travel history must include travel both within Canada as well as anywhere outside of Canada. One of the reasons behind this requirement is that certain geographic regions are considered by Health Canada and the US Centers for Disease Control and Prevention to be endemic for certain transmissible diseases. For this reason, a donor's history with respect to travel and residency could place them at higher risk for certain transmissible diseases, such as West Nile virus, malaria and yellow fever.

The following links contain information with respect to malaria endemic regions:

Public Health Agency of Canada:
https://travel.gc.ca/travelling/health-safety/travel-health-notices

US Centers for Disease Control (CDC):
http://www.cdc.gov/malaria/travelers/country_table/a.html

World Health Organization (WHO):
http://www.who.int/malaria/travellers/en/

In addition, Health Canada has issued measures to address the potential risk of Zika virus transmission through human cells, tissues and organs. A notice containing the measures can be found in Appendix 3.

Cases of donor allergies transferred to recipients have been reported for hematopoietic cell transplantation and solid organ transplantation, including potentially fatal allergies to nuts, seafood, penicillin and latex. In order to address this concern the medical social history requirements in section 12.2.2.3 of the organ standard have been amended to include information related to life threatening donor allergies. This information must be captured as part of the donor history in order to provide the necessary information to transplant establishments to allow them to take measures to address the possibility that the recipient could develop an allergy as a result of the transplant, particularly if the cause of death of the donor was due to an anaphylactic reaction related to exposure to an allergen.

To address the current medication requirement, establishments need to assess the donor for prescribed medications and other current medications, including any over the counter drugs or natural health products.

## Contraindications/Exclusionary Criteria

In addition to the exclusion criteria of section 13.1.3 of the general standard, donors shall be excluded from donating organs and islet cells on the basis of the exclusionary criteria in section 13.2.2 of the organ standard.

The donor's surgeon shall also assess the physical quality of the organ(s) to be donated. Any abnormality or concern, such as the presence of an unsuspected infection or malignancy, shall be documented, and all transplanting programs shall be immediately notified.

## Tests that are considered appropriate and effective

### Mandatory testing

In addition to tests for the disease or disease agents specified in section 14.2.6 of the general standard, Health Canada considers the following tests to be appropriate and effective for testing organ and islet cells donors in order to comply with section 14.2.6.3 of the organ standard:

a) serologic assays for the detection of antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and HTLV-II);
b) serologic assays for the detection of antibodies to toxoplasmosis for **heart** donors, which may be performed retrospectively by testing for antibody to toxoplasmosis in the donor's serum using a medically acceptable test (e.g., enzyme-linked immunoassay);
c) non-treponemal or treponemal-specific serologic assays for the detection of syphilis
d) serologic assays for the detection of IgG antibodies to cytomegalovirus [anti-CMV IgG or anti-CMV (total)]
e) serologic assays for the detection of antibodies to Epstein-Barr virus that are capable of detecting recent EBV infections as well as past infections (as determined acceptable by the source establishment and described in their SOPs). See recommended testing for EBV below for additional guidance on EBV testing.

Note that results of the tests for CMV, EBV, and toxoplasmosis may be reported following organ distribution.

Please refer to Table1 for timeframes for specimen collection.

### Recommended testing

Testing for WNV nucleic acid (WNV NAT) is recommended for organ and islet cell donors (section 14.2.6.4 of the organ standard). Anti-CMV IgM testing is also recommended.

An anti-viral capsid antigen IgG (anti-VCA IgG) test is recommended for the detection of EBV and could be supplemented with an anti-VCA IgM test to enhance detection of recent infections. Anti-EBV nuclear antigen (anti-EBNA IgG) IgG tests should be supplemented with appropriate EBV tests for enhanced early detection of EBV infection since EBNA IgG antibodies may not be detected in recently infected individuals.

Living organ donors should also be tested for HIV-1 and HCV using NAT, if available. In particular, NAT should be performed on organ donors (living and deceased) in circumstances where it is clinically indicated, for example, if a decision is made to use exceptional distribution for a CTO from a donor with a history of high risk behaviour and a negative serological test for HIV and HCV.

**Requirements for Imported Organs**

With regards to imported organs, the source establishment would be the foreign ODO. In some cases the foreign ODO may deal directly with the Canadian transplant establishment, who would not have to register as an importer since the transplant establishment is only importing for use in its own establishment. In some cases, a Canadian ODO may be involved in the process, but acting on behalf of the transplant establishment as a facilitator.

The transplant establishment and the Canadian ODO must clearly identify their respective roles and responsibilities with regards to imported organs within their SOPs. This includes identifying the information that the ODO must obtain on behalf of the transplant establishment in order for the transplant establishment to meet the requirements of Subsection 22(2) of the CTO Regulations.

Section 22(2) of the CTO Regulations provides an exception to organ standard provisions referenced in Section 22(1) of the CTO Regulations. It should be noted that Section 22(2) of the CTO Regulations does not exempt imported organs from general standard requirements referenced in Section 18 of the CTO Regulations, including ensuring that the testing requirements in section 14.2.6 of the general standard have been completed.

Requirements — lymphohematopoietic cells

**23.** (1) In assessing the suitability of a donor of lymphohematopoietic cells, an establishment must perform all of the following steps:

(a) obtain the donor information and history in accordance with sections 12.2.2.2 and 12.2.2.3 of the lymphohematopoietic standard;
(b) perform a physical examination of the donor in accordance with section 13.2 of the lymphohematopoietic standard;
(c) determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.1.3 of the lymphohematopoietic standard;
(d) perform the tests specified in section 12.2.2.4 of the lymphohematopoietic standard; and
(e) perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.3 of the lymphohematopoietic standard.

Exception — imported lymphohematopoietic cells

(2) Despite subsection (1), in the case of imported lymphohematopoietic cells, the source establishment must

(a) have documentation of the donor suitability assessment;
(b) perform the tests specified in section 12.2.2.4 of the lymphohematopoietic standard;
(c) perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.3 of the lymphohematopoietic standard; and
(d) determine that the donor is not unsuitable to donate on the basis of the exclusion criteria set out in section 13.1.3.4 of the lymphohematopoietic standard.

In the case of cord blood, the infant is considered the donor. Any testing that is to be done on the birth mother is referred to as surrogate testing.

Donor suitability assessment (section 12.2 of the lymphohematopoietic standard), which is intended to elicit risk factors, is generally based on a medical and social history, clinical status, physical examination and tests. Documentation of this assessment must include all the elements specified in section 12.2.2.3 of the lymphohematopoietic standard, and should also include all the elements in section 12.3 of the general standards, as specified in section 12.3 of the lymphohematopoietic standard.

## Donor Screening

Donor screening is one component of donor suitability assessment and is intended to elicit general health information and identify risk factors (e.g., infectious disease risks) that could potentially impact the safety of the lymphohematopoietic cells. This risk assessment is based on the donor's medical and social history, clinical status, physical examination and tests. The information regarding the donor's medical and social history and clinical status can be obtained through a donor interview and a review of the donor's medical records or charts. The interview should be conducted using a medical/sexual/social history questionnaire which includes the applicable contraindications/exclusion criteria and other relevant questions, and should be documented in the form of a checklist where the response/outcome for each criterion is recorded. In the case of a child donor, the interview may be carried out with one or more individuals who can provide the necessary information, such as the donor's parents or legal guardian. It is recommended that the interview take place in person or by telephone. It is also recommended that donor screening be performed as close to the time of retrieval as feasible. In the event that more than one month has elapsed since the donor screening questionnaire was completed and the retrieval has not yet occurred, Health Canada recommends reviewing the donor screening results with the donor as close to the time of retrieval as feasible in order to ascertain whether any of the information has changed. In such instances an abbreviated donor screening questionnaire would be acceptable provided it addresses all the necessary exclusion criteria.

An establishment must develop and maintain SOPs for all steps performed during donor screening, including those governing the conduct of the donor medical/sexual/social history interview and the administration of a donor screening questionnaire(s). If a questionnaire developed by a professional organization is to be used, an establishment must review the questionnaire to determine if it meets all the requirements of the CTO Regulations for donor screening.

Cases of donor allergies transferred to recipients have been reported for lymphohematopoietic cell transplantation and solid organ transplantation, including potentially fatal allergies to nuts, seafood, penicillin and latex. In order to address this concern the medical social history requirements in section 12.2.2.3.1 of the lymphohematopoietic cell standard have been amended to include information related to life threatening donor allergies. Except in the case of cord blood, this information must be captured as part of the donor history in order to be able to provide the necessary information for establishments to address the possibility that the recipient could develop an allergy as a result of the transplant.

The documentation of a donor's medical-social history shall include any travel outside the United States and Canada in the past three years to areas that are considered endemic for malaria by Health Canada or the US Centers for Disease Control (CDC). This information can be valuable when assessing donors for signs or symptoms of infection.

The following links contain information with respect to malaria endemic regions:

Public Health Agency of Canada:
https://travel.gc.ca/travelling/health-safety/travel-health-notices

US Centers for Disease Control (CDC):
http://www.cdc.gov/malaria/travelers/country_table/a.html

**World Health Organization (WHO):**
http://www.who.int/malaria/travellers/en/

In addition, Health Canada has issued measures to address the potential risk of Zika virus transmission through human cells, tissues and organs. A notice containing the measures can be found in Appendix 3.

Unless tested for WNV, a donor's travel history in the past 56 days must also be obtained with respect to any travel to WNV endemic areas, including WNV endemic areas within Canada, in order to comply with section 14.2.3 (d) (i) & (ii) of the lymphohematopoietic cell standard. A travel history within Canada is necessary during times of the year when WNV is potentially transmissible in Canada, and an establishment does not intend to perform WNV testing on donors who reside in regions of Canada that are not considered endemic for WNV.

## Contraindications/Exclusion Criteria

The conditions and behaviours set out in section 13.1.3 of the lymphohematopoietic standard and Annex E of the general standard may increase the risk that a donor may have and/or could potentially transmit an infectious disease to the recipient. For this reason, donors shall be excluded from donating lymphohematopoietic cells on the basis of these contraindications/exclusion criteria, except in cases where exceptional distribution is used (see sections 40 to 42 of the CTO Regulations for more information).

A first degree relative in the context of section 13.1.3 of the lymphohematopoietic standard refers to a genetic mother, father, sibling, or child of the recipient. Anybody that is not a first degree relative of the recipient must comply with the requirements of section 13.1.3.2 of the lymphohematopoietic standard. Section 13.1.3.2 requires that all allogeneic donors including cord blood donors, that are not first degree relatives of the recipient, be screened according to the criteria specified in Annex E of the general standard.

Examples of neurological diseases of unestablished etiology that are as listed as exclusion criteria in section 13.1.3 of the lymphohematopoietic standard include, but are not limited to, multiple sclerosis, Alzheimer's, Parkinson's and amyotrophic lateral sclerosis or Lou Gehrig's disease.

Examples of prion related disease as that are described as exclusion criteria in section 13.1.3 of the lymphohematopoietic standard include, but are not limited to, Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease and other transmissible spongiform encephalopathies.

For cord blood donors, first degree relatives include their genetic mother, father and siblings. Second degree relatives include the cord blood donor's genetic aunt, uncle, grandparent, or half-brother or sister.

As per section 13.1.3.3 of the lymphohematopoietic standard, a cord blood unit shall not be accepted for unrelated allogeneic use if there is a known family history of a genetic disease that could affect the recipient unless the risk has been excluded through donor testing or follow-up.

When enquiring about any family history of a genetic disease, it is recommended that the questions to the genetic mother be framed as "to the best of your knowledge" to account for the fact that a certain degree of uncertainty is to be expected when enquiring about medical information spanning generations.

In the event that the genetic or medical history of a first degree relative of the donor is completely unknown or unobtainable, including cases in which the donor was conceived from a sperm and/or egg donation, the cord blood unit should not be accepted as safe for transplantation. These units could, however, be collected and stored for release under Exceptional Distribution.

In the event that the genetic or medical history of a second degree relative of the donor is unknown or unobtainable, it is recommended that the source establishment have a process in place for disclosing this lack of information to the transplant program upon release of the unit. This situation might be encountered when one of the donor's parents was adopted and access to the medical and genetic history of his or her birth family is not available through adoption files or other means.

For allogeneic donations taking place outside of Canada donors shall be assessed and accepted by the collection facility and documentation of suitability shall be provided to the transplant establishment. A donor from outside of Canada shall be excluded if he or she has HIV, HBV, or HCV.

## Physical Examination

All donors must be given a physical exam which should assess for evidence of certain high risk behaviours (such as needle tracks or other signs of injection drug use), signs of bacterial, fungal, parasitic or viral infections of clinical significance and signs of malignancy.

Health Canada recommends that physical exams be performed as close to the time of retrieval as is reasonable and practical. Under normal circumstances, physical exams should be conducted within 30 days of the anticipated date of cell retrieval. If the retrieval of the cells is postponed, it will be left up to the clinical judgment of the source establishment to determine whether a repeat physical exam, or a limited repeat physical exam, is warranted. Such decisions can be delegated to the collection center physician.

If an examination of the donor was previously performed for other reasons, such as an assessment to determine if donation is safe for the donor, findings of such an examination can be reviewed and documented in the donor's records in lieu of a new physical examination, assuming the exam was performed within the recommended timeline. Such decisions can be delegated to the collection center physician.

In the case of cord blood, a surrogate physical examination of the birth mother of the donor must be performed and the results must be documented. If a physical examination was previously performed in the course of the birth mother's pregnancy, a review of the findings of such an examination can be performed and documented in the donor's records in lieu of a new physical examination, assuming the exam was performed within the recommended timeline.

An establishment must have SOPs describing the conduct of the physical examination of a donor.

## Donor Testing

### General Requirements

Donor testing includes, but is not limited to, laboratory tests for transmissible disease agents (e.g., HIV, HBV and HCV); tests performed to determine the donor's blood type (i.e., ABO group and Rh type) and HLA type; or any procedures done to evaluate or provide information on the lymphohematopoietic cells. The guidance provided below for donor testing focuses on HLA typing and laboratory tests for the various transmissible disease agents applicable to lymphohematopoietic cell donors.

Section 12.2.2.4.2 (e) and (f) of the lymphohematopoietic standard stipulates that cord blood HLA typing must be done at the time of banking and prior to release for unrelated allogeneic cord blood, whereas cord blood that is reserved for and restricted to potential allogeneic use in a relative of the donor need only be HLA typed prior to release. In the latter case, a second HLA typing to confirm the identity of the unit is not required if the initial HLA typing is performed after a recipient has been identified and the HLA typing is of sufficient resolution.

Units that have had confirmatory HLA typing performed on a contiguous segment at some point post freeze do not require repeat confirmatory testing prior to release from the cord blood bank.

### Time Frame for Specimen Collection

Infectious disease tests must be performed using blood specimens taken within seven days before collection or within seven days following collection of cord blood and within 30 days prior to the collection of all other donations, i.e., lymphohematopoietic cells derived from bone marrow and peripheral blood (subsection 12.2.2.4 of the lymphohematopoietic standard).

The collection of specimens within 30 days prior to the donation allows the determination of donor eligibility within the time frame required for the recipient to initiate myeloablative chemotherapy. In the event that collections from the same donor are performed more than 30 days apart, the donor shall be retested for the infectious disease markers, unless a previously positive test result has been documented.

**Table 2:** Timeframe for Specimen Collection for the Testing of Diseases or Disease Agents Specified in the Infectious Disease Testing Requirements of the Lymphohematopoietic Subset Standard

| Type of CTO | Type of Testing Required | Timeframe |
|---|---|---|
| Cord blood | serological screening tests and NAT for HIV-1 and HCV performed on the birth mother | within seven days before collection or within-seven days following collection |
| | WNV NAT performed on the birth mother | within seven days before collection or within-seven days following collection* |
| lymphohematopoietic cells (excluding cord blood) | serological screening tests performed on donor | within 30 days before collection (12.2.2.4.1) |
| | WNV NAT on donor | within 30 days before collection (12.2.2.4.1) |

*Given the transient nature of WNV viremia, Health Canada recommends that testing be performed on blood samples collected on the day of donation or as close to the time of donation as is feasible, taking into consideration WNV testing turnaround times. If this is not possible for cord blood donors and samples are collected after the donation, a WNV IgM test should be performed in addition to the WNV NAT in order to detect recent WNV infection in donors with negative WNV NAT results. It is acknowledged that similar to other infectious diseases, donors could become infected with WNV after sample collection but before donation if the samples are collected prior to donation. This could be addressed through additional screening and/or testing of samples collected on the day of donation.

Establishments must have SOPs that specify the time frames for the collection of blood specimens from donors of each type of lymphohematopoietic cells.

### Infectious Disease Testing

All source establishments are responsible for infectious disease testing, including testing which is carried out on its behalf by another establishment. They must have appropriate documentation (e.g., SOPs, agreements, contracts, or audit reports) to support that infectious disease testing is performed in accordance with the following:

1) Testing shall be performed by a laboratory that meets the applicable requirements of the authority having jurisdiction over that laboratory.
2) The tests for infectious diseases or disease agents that could lead to the exclusion of the donor (i.e., diseases or disease agents that are exclusion criteria under the CTO Regulations) must be performed using test kits that are licensed as required in sections 25 and 26 of the CTO Regulations. The tests for infectious diseases

or disease agents that do not lead to donor exclusion must be performed using test kits that are licensed as required in section 25.

3) The testing laboratories must follow the test kit manufacturer's instructions with respect to the following:
    a. the collection, handling, and storage of blood specimen;
    b. the time frame within which samples must be tested, if applicable;
    c. the procedure for testing; and
    d. the interpretation of the test results.

### Interpretation of Infectious Disease Test Results

The terms used by test kit manufacturers for the interpretation of serological test results are determined in part, by the testing algorithms used. In general, the initial serological screening test is performed using a single blood sample. A nonreactive sample is considered a negative test result and further testing is not required. In contrast, a reactive sample is considered initially reactive instead of positive because (1) the sample has to be retested in duplicate using the same test but not necessarily the same lot; and (2) the results are considered repeatedly reactive if either one of the two replicates is reactive. These two additional steps are necessary to achieve the final outcome (i.e. "positive" or "negative") of the test kit in the event that a sample is initially reactive. It is important to note that this testing algorithm is intended to serve only as an example and establishments must always apply the specific testing algorithm proposed by each test kit manufacturer.

It should also be noted that some test kit manufacturers may only consider a sample to be positive once confirmatory or supplemental testing with a different test kit is performed to confirm the results of the first test kit. While confirmatory testing is necessary for patient diagnosis, it should not be considered for the purpose of donor screening because false negative confirmatory test results cannot be ruled out. Thus, in these circumstances, donors must still be excluded regardless of the results of confirmatory tests.

Establishments that use third party testing labs must ensure that, in cases where confirmatory testing is performed for patient diagnosis, they are provided the results of the initial test kit in order to be able to make the appropriate determination of donor eligibility.

In addition, some test kit manufacturers do not use the term "repeatedly reactive" for the final outcome of a particular screening or diagnostic test. Instead, they use the terms "reactive" or "positive" for the final outcome of these tests.

In this guidance document:

1) A negative test result means the final outcome in which the test specimen is determine to be nonreactive by the test kit manufacturer.
2) A positive test result means the final outcome in which the test specimen is determined to be "reactive", "repeatedly reactive" or "positive" according to the testing algorithms proposed by the test kit manufacturer.
3) A confirmed positive test result means the outcome of a confirmatory or supplemental test performed using a different test kit, in which the tested specimen is determined to be reactive.

Donor eligibility determination shall include the interpretation of the infectious disease test results as outlined below:

1) For HIV-1 and 2, HBV, HCV and HTLV-I and II, lymphohematopoietic cells shall not be released for transplantation if the donor's specimen is positive for any of the infectious disease markers specified in this document. In cases where additional tests are performed to confirm or supplement the positive test results (e.g., for the purpose of donor or next-of-kin notification), lymphohematopoietic cells shall not be released for transplantation, unless the exceptional distribution provisions are met, even if the confirmatory or supplemental test results are negative.

2) Regarding syphilis testing, lymphohematopoietic cells may be released for transplantation if the donor's blood sample is positive using a nontreponemal test, but negative using a treponemal-specific confirmatory assay. It should be noted that if establishments decide to use a treponemal-specific assay for syphilis as the test of record, the lymphohematopoietic cells shall not be released for transplantation if the donor's specimen is positive unless the exceptional distribution provisions are met. This is because a positive treponemal-specific test identifies both recent syphilis infections, and remote or treated syphilis infections. While a nontreponemal test can be performed to rule out a recent infection, false negative results cannot be ruled out. Thus, appropriate testing algorithms need to be developed to resolve this issue.
3) If an establishment performs additional tests that are not mandatory (e.g., NAT for HIV-1 or HCV for unbanked cells) the results must be taken into consideration when determining donor eligibility if they are available prior to the release of the lymphohematopoietic cells.
4) For cytomegalovirus (CMV) and Epstein-Barr virus (EBV), the cells may be released for distribution if a donor's blood sample is positive, or if the test results are pending. It is not necessary to use exceptional distribution under these circumstances. The test results for these infectious agents may be important when selecting cells for specific patients and can impact recipient monitoring protocols. These results must be communicated to the transplant physicians.

If a donor's specimen tests positive for HIV, HBV or HCV using a required serological test, but is found to be negative using NAT the cells cannot be distributed, unless done under exceptional distribution.

It should be noted that, in uncommon circumstances, exceptional distribution may be used if the donor specimen is repeatedly reactive or positive for the markers of infectious disease agents. More information on exceptional distribution can be found in sections 40 to 42 of the CTO Regulations.

Results of all tests, including those that are optional, must be included in the donor records. Establishments must have SOPs for the interpretation and handling of all test results, including the communication of test results to transplant physicians or to establishments to which the lymphohematopoietic cells are distributed. Procedures must also be established for handling the results of optional tests that become available after the lymphohematopoietic cells have been released for distribution, and must include notification of transplant physicians or establishments to which the lymphohematopoietic cells are distributed.

#### Archived Samples

The CTO Regulations do not require the collection of samples for archiving as this has no impact on the safety of lymphohematopoietic cells that meet current regulatory requirements. It is recommended that cell, tissue, plasma or serum samples from each donor be archived for retrospective testing of donors of lymphohematopoietic cells that are still in inventory when new tests are adopted for screening donors for existing or emerging pathogens. The requirement for such retrospective testing will be based on the degree of safety enhancement afforded by the new tests, and the availability of tests that are appropriately validated or approved under the MDR for testing frozen specimens. If such retrospective testing is required, Health Canada will inform CTO establishments.

If an establishment chooses to archive samples, they must have SOPs for the collection and storage of samples for archiving. Samples must be stored frozen, and should be kept for at least 5 years. Establishments must also have documentation to show that the samples are maintained at the appropriate temperature throughout the storage period.

### Tests that are considered appropriate and effective

#### Mandatory Testing

All donors of lymphohematopoietic cells must be tested for the infectious disease agents listed in section 14.2.3 of the lymphohematopoietic standards, using appropriate and effective tests. A test is considered appropriate and effective if (i) it is licensed for the detection of the infectious disease agent or marker in accordance with the licensing requirements specified in sections 25 and 26 of the CTO Regulations; (ii) it is used in accordance with the test kit manufacturer's instructions; and (iii) it is used for the detection of an infectious disease marker that is relevant at the time testing is performed. A list of such appropriate infectious disease markers is provided below (see Appendix 2 also for a complete list of all required and recommended tests). This list may be revised when new infectious disease tests become licensed, or when new information necessitates an amendment.

Health Canada considers the following tests to be appropriate and effective for testing lymphohematopoietic cell donors in order to comply with section 14.2.3 of the lymphohematopoietic standard:

a) serologic assays for the detection of antibodies to the human immunodeficiency virus, types 1 and type 2 (anti-HIV-1 and anti-HIV-2);
b) serologic assays for the detection of hepatitis B surface antigen (HBsAg);
c) serologic assays for the detection of total antibody to hepatitis B core antigen (anti-HBc, IgG and IgM)
d) serologic assays for the detection of antibodies to hepatitis C virus (anti-HCV)
e) serologic assays for the detection of antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and anti-HTLV-II)
f) serologic assays for the detection of IgG antibodies to cytomegalovirus [anti-CMV IgG or anti-CMV (total)]
g) non-treponemal or treponemal-specific serologic assays for the detection of syphilis
h) assays for the detection of West Nile Virus (WNV) nucleic acid (if the donation falls within the time frames for seasonal testing, or if there are other circumstances that would lead to testing outside of those time frames, e.g., if a donor has travelled to an area where WNV is endemic)
i) nucleic acid testing (NAT) for the detection of HIV-1 for banked lymphohematopoietic cell donations (i.e., cord blood donations)
j) nucleic acid testing (NAT) for the detection of HCV for banked lymphohematopoietic cell donations (i.e., cord blood donations)

In the case of infant donors, the birth mother must be tested for infectious disease agents, in order to address vertical transmission of infectious agents from the birth mother to a donor who is less than 18 months old, or to a donor who was breastfeeding at any time during the 12 months prior to donation (section 14.2.6.2 of the general standard).

However, the mother of an infant donor who is 29 days or older need not be tested for infectious disease agents, if testing of the infant donor includes the serological tests listed above as well as NAT for HIV-1 and HCV.

In the case of donated cord blood, surrogate testing of the birth mother need only be performed.

The establishments must have SOPs that describe which infectious disease tests must be performed and when testing of the birth mother is required for infant donors.

Lymphohematopoietic cell donors shall be tested for WNV using a test kit that has been licensed for the detection of viral nucleic acid. Testing could be performed on a seasonal basis if specific procedures are in place to determine the time frames for seasonal testing and to determine other circumstances when testing for WNV may be required outside of these time frames (i.e., when a donor has travelled to an endemic area).

A test kit has been licensed by Health Canada for the detection of WNV ribonucleic acid in plasma specimens from both living and deceased donors.

The minimum donor testing requirements stated in section 12.2.2.4 of the lymphohematopoietic standard have to be met before transplantation.

### Recommended Testing

It is recommended that donors of unbanked lymphohematopoietic cells also be tested for HIV-1 and HCV using NAT, if available. In particular, NAT should be performed in circumstances where it is clinically indicated, for example, if a decision is made to use exceptional distribution for lymphohematopoietic cells from a donor with a history of high risk behaviour and a negative serological test for HIV and HCV.

The Medical Device Bureau of the Therapeutic Products Directorate is the Canadian federal regulator responsible for licensing in accordance with the F&DR and the MDR. The Medical Devices Active Licence Listing (MDALL) active licences database contains all licensed Class II, Class III and Class IV Medical Devices for sale in Canada, and can be found on the Health Canada Web site. On the medical devices active licence listing page, select Active Licence Search and a device can be found by company name, licence name device name, company ID or licence number.

Retrieval interval — tissues

**24.** An establishment that retrieves tissue from a deceased donor must carry out the retrieval within the scientifically based maximum interval between the cardiac asystole of the donor and the retrieval of the tissue.

The maximum interval between the cardiac asystole of the donor and the retrieval of the tissue is considered scientifically based if it meets one or more of the following criteria:

a) the maximum interval between the cardiac asystole of the donor and the retrieval of the tissue has been established in standards developed by recognized professional organizations, based on established practice;
b) data is available in the scientific literature to support the maximum interval between the cardiac asystole of the donor and the retrieval of the tissue;
c) the maximum interval between the cardiac asystole of the donor and the retrieval of the tissue has been validated by the establishment.

Licensed diagnostic devices

**25.** (1) Subject to subsection (2), in vitro diagnostic devices that are used by an establishment in the testing of donor blood for transmissible disease agents or markers under these Regulations must be licensed either

(a) in Canada, if the testing is performed in Canada; or
(b) in Canada or the United States, if the testing is performed outside Canada.

Exception — lymphohematopoietic cells

(2) In the case of lymphohematopoietic cells that are imported into Canada for transplantation into a specific recipient, the in vitro diagnostic devices may be licensed in Canada or any other jurisdiction.

Under subsection 25(1) of the CTO Regulations, the in vitro diagnostic devices that are used by an establishment to test donors of CTO for transmissible diseases or disease agents must be licensed in Canada, if the testing is carried out in Canada. If the testing is performed outside of Canada, the in vitro diagnostic devices must be licensed either in Canada or the United States. An exception is made in subsection 25(2) for lymphohematopoietic cells that are imported into Canada for transplantation into a specific recipient, where the in vitro diagnostic devices used in donor testing may be licensed in Canada or any other jurisdiction.

The Medical Device Bureau of Health Canada's Therapeutic Products Directorate is the Canadian federal regulator responsible for licensing in accordance with the F&DR and the MDR.

The Medical Devices Active Licence Listing (MDALL) is a database containing all licensed Class II, Class III and Class IV Medical Devices for sale in Canada, can be found on the Health Canada Web site.

In vitro diagnostic devices — cells and tissues

**26.** (1) In the case of cells and tissues, in vitro diagnostic devices that are used by an establishment in the testing of donor blood for transmissible disease agents or markers under these Regulations must be licensed for screening donors.

Exception — syphilis

(2) Despite subsection (1), in vitro diagnostic devices that are used in the testing of donor blood for syphilis may be licensed either for diagnosis or screening donors.

Donor screening test kits are licensed based on investigational testing in a population with a low disease prevalence (e.g., healthy blood donors), with an emphasis on test sensitivity. In contrast, investigational testing of test kits that are licensed for diagnosis is performed in a symptomatic population, with an emphasis on test specificity. Thus, test kits that are licensed for donor screening are considered more appropriate for screening CTO donors.

Health Canada has determined that the requirement to use tests that are licensed for screening donors (as opposed to tests that are licensed for diagnostic purposes) is not necessary in the case of tests intended to detect the presence of a disease or disease agent in a donor that is not considered a contraindication to donation (e.g., Cytomegalovirus (CMV) testing of lymphohematopoietic cell donors).

Therefore, Health Canada intends to amend section 26 (1) to only require assays that are licensed for screening donors for diseases or disease agents that are exclusion criteria to donation under the CTO Regulations. This will allow establishments to use assays that are either licensed for diagnostic purposes or for screening donors when testing donors for diseases or disease agents that are not exclusion criteria under the CTO Regulations.

In the interim period, Health Canada will assign a low priority to enforcement actions for establishments that are using assays licensed for diagnostic purposes when testing donors for diseases or disease agents that are not exclusion criteria under the CTO Regulations. In addition, establishments will not be required to use exceptional distribution in these circumstances.

In the case of tissues and cells, with the exception of islet cells, the diagnostic devices that are used by an establishment to test for diseases or disease agents that are exclusion criteria under the CTO Regulations, must be licensed for screening donors. Infectious disease test kits that are used in the case of organ donors may be licensed for either screening donors or for diagnosis, as the time frames for organ transplantation don't always permit the use of screening tests. The CTO Regulations also provide for the use of test kits licensed for diagnosis in the case of syphilis testing.

Infectious disease tests are also licensed for different types of specimens, and the test kit manufacturers provide instructions for the use of each test kit in the package insert. In the context of CTO donations, a test may be licensed for testing blood specimens obtained from live donors (i.e., the blood specimen is obtained while the donor's heart is still beating), or from cadaveric donors (i.e., the blood specimen is obtained after the donor's heart stops beating). For specimens obtained after the donor's heart stops beating, establishments should use a test that is specifically licensed for cadaveric specimens, if such tests are available in the jurisdiction where the test is being performed.

Bacteriological testing — tissues

**27.** An establishment that retrieves tissue, except ocular tissue, must perform bacteriological testing in accordance with section 14.3 of the tissue standard, except for section 14.3.2.8.

## Source Establishment Requirements

The source establishment must ensure that laboratories performing microbial testing meet the applicable requirements of the authorities having jurisdiction. A copy of the laboratory's most recent certificate of accreditation would fulfill this requirement.

### Testing Establishment Requirements

Laboratories must ensure that microbial testing is performed in accordance with validated procedures by qualified staff and that the test results are documented in the donor's record. In addition, all methods, materials and equipment shall be suitable for their intended use and lot numbers, expiry dates and other relevant information should be recorded.

Indirect or direct sampling methods may be used to obtain microbial culture test samples. Samples may either be collected from each individual tissue or may be obtained using a sampling strategy that represents all the tissues received from a particular donor.

Indirect sampling can be accomplished by either a swabbing method or a fluid extraction method. Direct sampling is usually accomplished by placing samples of tissue directly into growth media.

Quality control (QC) testing must be performed for any transport medium prepared in-house to ensure it maintains the viability of both aerobic and anaerobic organisms. Similarly, growth media prepared in-house must be subject to QC testing to ensure its sterility as well as its ability to support the growth of aerobic and anaerobic organisms.

Tissue sampling and test methods shall be evaluated for sensitivity and found to be appropriate and effective for each tissue type recovered and processed.

All testing methods and protocols must be documented in the establishment's standard operating procedures (SOP).

Establishments may find it helpful to consult the AATB Guidance Document: Microbiological Process Validation & Surveillance Program and CBS Leading Evidence Based Practice Guidelines for: Tissue Recovery, Microbial Sampling, Processing of Musculoskeletal Tissue, Processing of Cardiac Tissue and Processing of Skin Tissue when reviewing or updating established microbiological sampling plans and microbiological test methods.

## Packaging and Labelling (Sections 28 to 33 of the CTO Regulations)

Packaging materials

**28.** An establishment that packages cells, tissues or organs must ensure that it uses appropriate packaging materials that are free from damage and capable of maintaining the integrity of the cells, tissues and organs.

An establishment must have documented evidence that the packaging materials used are capable of maintaining the integrity of the CTO. The documented evidence must be available upon request. Evidence could consist of specification sheets, certificates of analysis (COAs), or manufacturer's package inserts describing the packaging material.

The packaging materials must also be compatible with the CTO in order to prevent any interactions which may cause the package to degrade or chemicals from the packaging to be absorbed by the CTO. Only packaging materials assessed and released by Quality Assurance (QA) personnel or by a designated alternate should be used in the packaging of CTO. Any changes in the packaging materials must be approved by the QA personnel or the designated alternate prior to use. Materials that are outdated or rejected should be adequately segregated until their disposal, which should be recorded. All packaging materials must be visually inspected.

Language requirement

**29.** All of the information that is required by these Regulations to appear on a label or package insert must be in either English or French.

Cells, except islet cells

**30.** (1) An establishment that distributes cells, except islet cells, must ensure that all of the applicable information, as indicated by an "X", set out in the table to this subsection is provided on the interior label, in the package insert and on the exterior label.

Pancreas and islet cells

(2) An establishment that distributes a pancreas for islet cell transplantation, or islet cells, must ensure that all of the applicable information, as indicated by an "X", set out in the table to this subsection is provided on the interior label, in the package insert and on the exterior label.

The interior label is the label that is affixed to the interior package, which is the innermost package of a cell, tissue, or organ that has a non-sterile exterior.

The package insert is the document that is prepared by the source establishment to accompany a cell, tissue or organ.

The exterior label is the label that is affixed to the exterior package, which is the outermost package in which a cell, tissue or organ is delivered, transported or shipped in.

## TABLE TO SUBSECTION 30(1)
## LABELLING REQUIREMENTS FOR CELLS, EXCEPT ISLET CELLS

| | Column 1 | Column 2 From retrieval establishment to transplant establishment | | | Column 3 From retrieval establishment to cell bank | | | Column 4 From cell bank to any other establishment | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Item | Required information | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label |
| **Information about donor and cell** | | | | | | | | | | |
| 1. | Name of cell | X | X | | X | X | | X | X | |
| 2 | Description of cell | | X | | | X | | | X | |
| 3. | Donor identification code, clearly labelled as such | X | X | | | | | X | X | |
| 4. | Information capable of identifying the donor | | | | X | X | | | | |
| 5 | Donor assessment record | | | | | X | | | | |
| 6. | ABO group and Rh factor of donor, if applicable | X | X | | X | X | | X | X | |
| 7. | The hazard pictogram entitled "Biohazardous Infectious Material" set out in Schedule 3of the Hazardous Products Regulations, if applicable | X | | X | X | | X | X | | X |

|  | Column 1 | Column 2 From retrieval establishment to transplant establishment |  |  | Column 3 From retrieval establishment to cell bank |  |  | Column 4 From cell bank to any other establishment |  |  |
|---|---|---|---|---|---|---|---|---|---|---|
| Item | Required information | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label |
| **Retrieval information** |  |  |  |  |  |  |  |  |  |  |
| 8. | Date, time and time zone of retrieval |  | X |  |  | X |  |  |  |  |
| 9. | Information specific to retrieval procedure |  | X |  |  | X |  |  |  |  |
| **Processing information** |  |  |  |  |  |  |  |  |  |  |
| 10. | Name of anticoagulant and other additive, if applicable |  | X |  |  | X |  |  | X |  |
| 11. | Statement "For Autologous Use Only", if applicable | X | X |  | X | X |  | X | X |  |
| **Information for transplant establishment** |  |  |  |  |  |  |  |  |  |  |
| 12. | Statement that the cell has been declared safe for transplantation |  |  |  |  |  |  |  | X |  |
| 13. | Statement "For Exceptional Distribution", if applicable |  | X |  |  |  |  |  | X |  |
| 14. | If applicable, the reasons for exceptional distribution and a statement of how the cell does not meet the requirements of these Regulations |  | X |  |  |  |  |  | X |  |
| 15. | Instructions on how to report errors, accidents and adverse reactions |  |  |  |  |  |  |  | X |  |
| 16. | Expiry date and time, if applicable |  |  |  |  |  |  | X | X |  |
| **Establishment information** |  |  |  |  |  |  |  |  |  |  |
| 17. | Name of retrieval establishment, its civic address and contact information |  | X | X |  | X | X |  |  |  |
| 18. | Name of source establishment, its civic address and contact information |  | X | X |  | X | X |  | X | X |
| 19. | Registration number of source establishment, clearly labelled as such |  | X | X |  |  |  |  | X | X |
| 20. | Name of transplant establishment, if known, its civic address and contact information |  |  | X |  |  |  |  |  | X |
| **Storage information** |  |  |  |  |  |  |  |  |  |  |
| 21. | Statement "Human cells for transplant" |  |  | X |  |  | X |  |  | X |
| 22. | Handling instructions |  |  | X |  |  | X |  |  | X |

| Item | Column 1 | Column 2<br>From retrieval establishment to transplant establishment | | | Column 3<br>From retrieval establishment to cell bank | | | Column 4<br>From cell bank to any other establishment | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Item | Required information | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label |
| | | | | | | | | | | |
| | for storage and for storage during transportation | | | | | | | | | |

## TABLE TO SUBSECTION 30(2)
## LABELLING REQUIREMENTS FOR PANCREAS AND ISLET CELLS

| Item | Column 1 | Column 2<br>PANCREAS: From retrieval establishment to source establishment | | | Column 3<br>ISLET CELLS: From source establishment to any other establishment | | |
|---|---|---|---|---|---|---|---|
| Item | Required information | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label |
| | | | | | | | |
| **Information about donor and organ or islet cells** | | | | | | | |
| 1. | Name of organ or cells, as applicable | X | X | | X | X | |
| 2. | Description of organ or cells, as applicable | | X | | | X | |
| 3. | Donor identification code, clearly labelled as such | | | | X | X | |
| 4. | Information capable of identifying the donor | X | X | | | | |
| 5. | Donor assessment record | | X | | | | |
| 6. | ABO group and Rh factor of donor, if applicable | X | X | | X | X | |
| 7. | The hazard pictogram entitled "Biohazardous Infectious Material" set out in Schedule 3of the Hazardous Products Regulations, if applicable | X | | X | X | | X |
| **Retrieval information** | | | | | | | |
| 8. | Date, time and time zone of asystole or aortic clamping, if applicable | | X | | | | |
| 9. | Date, time and time zone of retrieval | | X | | | | |
| 10. | Information specific to retrieval procedure | | X | | | | |
| 11. | Name of perfusion solution | | X | | | | |
| **Processing information** | | | | | | | |
| 12. | Name of storage solution | | X | | | | |
| 13. | Name of additives, if applicable | | | | | X | |
| **Information for establishments** | | | | | | | |
| 14. | Statement that the cells have been declared safe for transplantation | | | | | X | |
| 15. | Statement "For Exceptional Distribution", if applicable | | X | | X | X | |
| 16. | If applicable, the reasons for exceptional distribution and a statement of how the organ or cells do not meet the requirements of these Regulations | | X | | | X | |
| 17. | Instructions on how to report errors, accidents and adverse reactions | | X | | | X | |
| 18. | Expiry date and time, if applicable | | | | X | X | |
| **Establishment information** | | | | | | | |
| 19. | Name of retrieval establishment, its civic address and contact information | | X | X | | X | X |
| 20. | Name of source establishment, its civic | | X | X | | X | X |

| | Column 1 | Column 2<br>PANCREAS: From retrieval establishment to source establishment | | | Column 3<br>ISLET CELLS: From source establishment to any other establishment | | |
|---|---|---|---|---|---|---|---|
| Item | Required information | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label |
| | | | | | | | |
| | address and contact information | | | | | | |
| 21. | Registration number of source establishment, clearly labelled as such | | X | X | | X | X |
| 22. | Name of other establishment, its civic address and contact information | | | | | | X |
| **Storage information** | | | | | | | |
| 23. | Statement "Human organ for transplant" or "Human cells for transplant", as applicable | | | X | | | X |
| 24. | Handling instructions for storage and for storage during transportation | | | X | | | X |

The donor identification code must appear clearly on the product label and all product labels must include information to enable traceability back to the donor.

## Information capable of identifying the donor

This kind of information refers to any information that allows the cell bank or appropriate establishment to identify the donor. It includes, but is not limited to, the donor's name, date of birth, hospital identification number and health care number.

## Information specific to the retrieval procedure

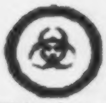
Abnormal or noteworthy findings in the donor that are identified at the time of retrieval shall be listed in the package insert when the cells are distributed from a retrieval establishment to a transplant establishment or a cell bank.

For cord blood, the type of delivery and any relevant details regarding the delivery shall be listed as well as the method of cord blood retrieval.

The lot numbers of any solutions used during transport of the cells should also be listed on the package insert.

## Biohazardous Infectious Materials

The pictogram that is to be used for biohazardous infectious materials is the following:



This pictogram must appear on the interior and exterior labels of CTO that have tested positive for infectious diseases markers that would lead to the exclusion of a donor. In the case where the tests have not yet been performed or the results are not yet known, the pictogram should not be used.

If a generic CTO package insert is prepared, all information specific to a CTO could be printed on a label that will accompany the CTO "standard" package insert.

In situations where no exterior packaging is used, the required information for the exterior label must be included on the interior label or package insert.

CTO should either be labelled as safe for transplantation or "for exceptional distribution" but not both.

Tissues

**31.** An establishment that distributes tissues must ensure that all of the applicable information, as indicated by an "X", set out in the table to this section is provided on the interior label, in the package insert and on the exterior label.

## TABLE TO SECTION 31
## LABELLING REQUIREMENTS FOR TISSUE

| Item | Column 1 Required information | Column 2 From retrieval establishment to tissue bank | | | Column 3 From tissue bank to any other establishment | | |
|---|---|---|---|---|---|---|---|
| | | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label |
| **Information about donor and tissue** | | | | | | | |
| 1. | Name of tissue, and whether left or right side, if applicable | X | X | | X | X | |
| 2. | Description of tissue | | X | | | X | |
| 3. | Donor identification code, clearly labelled as such | | | | X | X | |
| 4. | Information capable of identifying the donor | X | X | | | | |
| 5. | Donor assessment record | | X | | | | |
| 6. | The hazard pictogram entitled "Biohazardous Infectious Material" set out in Schedule 3of the Hazardous Products Regulations, if applicable | X | | X | X | | X |
| **Retrieval information** | | | | | | | |
| 7. | Date, time and time zone of asystole or aortic clamping, if applicable | | X | | | | |
| 8. | Date, time and time zone of retrieval | | X | | | | |
| 9. | Information specific to retrieval procedure | | X | | | | |
| **Processing information** | | | | | | | |
| 10. | Name of storage solution, if applicable | | X | | | X | |
| 11. | Name of anticoagulant and other additive, if applicable | | | | | X | |
| 12. | Statement that the tissue has been irradiated, if applicable | | | | X | X | |
| 13. | Description of the disinfection and sterilization processes that were used, if applicable | | | | | X | |
| 14. | Statement "For Autologous Use Only", if applicable | X | X | | X | X | |
| **Information for transplant establishment** | | | | | | | |
| 15. | Tissue-specific instructions for preparation for use, if applicable | | | | | X | |
| 16. | Statement that the tissue has been declared safe for transplantation | | | | | X | |
| 17. | Statement "For Exceptional Distribution", if applicable | | | | X | X | |
| 18. | If applicable, the reasons for exceptional distribution and a statement of how the tissue does not meet the requirements of these Regulations | | | | | X | |
| 19. | Instructions on how to report errors, accidents and adverse reactions | | | | | X | |
| 20. | Expiry date and time, if applicable | | | | X | X | |
| **Establishment information** | | | | | | | |
| 21. | Name of retrieval establishment, its civic address | | X | X | | | |

| Item | Column 1 | Column 2 From retrieval establishment to tissue bank | | | Column 3 From tissue bank to any other establishment | | |
|---|---|---|---|---|---|---|---|
| | Required information | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label |
| | | | | | | | |
| | and contact information | | | | | | |
| 22. | Name of source establishment, its civic address and contact information | | X | X | | X | X |
| 23. | Registration number of source establishment, clearly labelled as such | | | | | X | X |
| 24. | Name of transplant establishment, if known, its civic address and contact information | | | | | | X |
| **Storage information** | | | | | | | |
| 25. | Statement "Human tissue for transplant" | | | X | | | X |
| 26. | Handling instructions for storage and for storage during transportation | | | X | | | X |

The donor identification code must appear clearly on the product label and all product labels must include information to enable traceability back to the donor.

## Information capable of identifying the donor

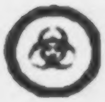
This kind of information refers to any information that allows the tissue bank to identify the donor. It includes, but is not limited to, the donor's name, date of birth, hospital identification number and health care number.

## Information specific to the retrieval procedure

Any abnormal or noteworthy findings in the donor that are identified at the time of retrieval should be listed in the package insert when the tissue is distributed from a retrieval establishment to a tissue bank. The lot numbers of any solutions used during transport of the tissue should also be listed on the package insert.

## Biohazardous Infectious Materials

The pictogram that is to be used for biohazardous infectious materials is the following:



This pictogram must appear on the interior and exterior labels of CTO that have tested positive for infectious diseases markers that would lead to the exclusion of a donor. In the case where the tests have not yet been performed or the results are not yet known, the pictogram should not be used.

If a generic CTO package insert is prepared, all information specific to a CTO could be printed on a label that will accompany the CTO "standard" package insert.

In situations where no exterior packaging is used, the required information for the exterior label must be included on the interior label or package insert.

CTO should either be labelled as safe for transplantation or "for exceptional distribution" but not both.

When transporting tissue from a retrieval establishment to a tissue bank, establishments can add statements such as "further processing required" in addition to the labelling requirement to state "Human Tissue for transplant", under item #25. This type of additional statement, or other similar statements, will help reflect that the tissue has not yet been determined safe for transplant. Health Canada recommends that establishments avoid using statements on the label that indicate that the package contains human tissue that is **not** for transplant, unless further clarification is provided that reduces the possibility of confusion regarding the final intended purpose of the tissue.

**Organs**

**32.** An establishment that distributes organs must ensure that all of the applicable information, as indicated by an "X", set out in the table to this section is provided on the interior label, in the package insert and on the exterior label.

| | Column 1 | Column 2 DECEASED DONOR: From retrieval establishment to transplant establishment | | | Column 3 LIVING DONOR: From retrieval establishment to transplant establishment | | |
|---|---|---|---|---|---|---|---|
| Item | Required information | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label |
| **Information about donor and organ** | | | | | | | |
| 1. | Name of organ, and whether left or right side, if applicable | X | X | X | X | X | |
| 2. | Description of organ | | X | | | X | |
| 3. | Donor identification code, clearly labelled as such | X | X | | X | X | |
| 4. | All information in the donor assessment record that is not capable of identifying the donor | | X | | | | |
| 5. | ABO group and Rh factor of donor | X | X | | X | X | |
| 6. | The hazard pictogram entitled "Biohazardous Infectious Material" set out in Schedule 3of the Hazardous Products Regulations, if applicable | X | | X | X | | X |
| **Retrieval information** | | | | | | | |
| 7. | Date, time and time zone of asystole or aortic clamping, if applicable | | X | | | | |
| 8. | Date, time and time zone of retrieval | | X | | | X | |
| 9. | Information specific to retrieval procedure | | X | | | X | |
| 10. | Name of perfusion solution | | X | | | X | |
| **Processing information** | | | | | | | |
| 11. | Name of storage solution | | X | | | X | |
| **Information for transplant establishment** | | | | | | | |
| 12. | Statement that the organ has been declared safe for transplantation | | X | | | | |
| 13. | Statement "For Exceptional Distribution", if applicable | X | X | | X | X | |
| 14. | If applicable, the reasons for exceptional distribution and a statement of how the organ does not meet the requirements of these Regulations | | X | | | X | |
| 15. | Instructions on how to report errors, accidents and adverse reactions | | X | | | X | |
| **Establishment information** | | | | | | | |
| 16. | Name of retrieval establishment, its civic address and contact information | | X | X | | X | X |
| 17. | Name of source establishment, its civic address and contact information | | X | X | | X | X |
| 18. | Registration number of source establishment, clearly labelled as such | | X | X | | X | X |
| 19. | Name of transplant establishment, its civic address and contact information | | | X | | | X |
| **Storage information** | | | | | | | |
| 20. | Statement "Human organ for transplant" | | | X | | | X |

| | Column 1 | Column 2<br>DECEASED DONOR: From retrieval establishment to transplant establishment | | | Column 3<br>LIVING DONOR: From retrieval establishment to transplant establishment | | |
|---|---|---|---|---|---|---|---|
| Item | Required information | Interior label | Package insert | Exterior label | Interior label | Package insert | Exterior label |
| 21. | Handling instructions for storage and for storage during transportation | | | X | | | X |

The donor identification code must appear clearly on the product label and all product labels must include information to enable traceability back to the donor.

## All information in the donor assessment record that is not capable of identifying the donor

The donor assessment record should be redacted in order to remove any information that is capable of precisely identifying the donor. Information that can directly identify the donor must not be included in the recipients chart due to privacy issues and is therefore not included on the labels that accompany the organ from the retrieval establishment to the transplant establishment.

## Information specific to the retrieval procedure

The following information related to the donors condition during retrieval of the organ (some of which will not apply to living donors) should be listed in the package insert when an organ is distributed from a retrieval establishment to a transplant establishment:

- hemodynamic stability (vital signs)
- blood products or fluids administered
- oxygenation levels
- relevant blood work results
- any abnormal or noteworthy findings in the donor that are identified at the time of retrieval
- the lot numbers of any perfusion solutions or solutions used during transport of the organ should also be listed on the package insert.

It is acknowledged that additional information may not come to light until all of the organs have been retrieved; therefore, it is acceptable to electronically transfer (e.g., fax or email) additional information when the organ is already in transport.

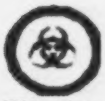
## Statement that the organ has been declared safe for transplantation

CTO should either be labelled as safe for transplantation or "for exceptional distribution" but not both.

As an alternative to stating directly on the label that the "organ has been declared safe for transplantation", Health Canada will accept alternative wording that indicates that the organ has been processed according to the CTO Regulations and that no contraindications to donation have been identified.

## Biohazardous Infectious Materials

The pictogram that is to be used for biohazardous infectious materials is the following:



This pictogram must appear on the interior and exterior labels of CTO that have tested positive for infectious diseases markers that would lead to the exclusion of a donor. In the case where the tests have not yet been performed or the results are not yet known, the pictogram should not be used.

If a generic CTO package insert is prepared, all information specific to a CTO could be printed on a label that will accompany the CTO "standard" package insert.

In cases where the CTO is not packaged, for example when organ retrieval and transplantation are performed simultaneously or sequentially in the same or adjacent operating room, the information that, in other circumstances, must appear on the interior label, the package insert and on the exterior label must be recorded elsewhere. This could be achieved by recording the information in a document that accompanies the organ.

> Additional information required
> **33.** A registered establishment that imports and distributes, or that only distributes, a cell or tissue must ensure that the following information is added to that required by sections 30 and 31:
> (a) on the exterior label and in the package insert, the name of the establishment, its civic address and contact information; and
> (b) on the exterior label and in the package insert, the establishment's registration number.

If the establishment that imports and distributes does not take physical possession of the cells or tissues at any point (e.g., the cells or tissues are sent directly to the transplant establishment from the source establishment), its name and registration number is not required to appear on the exterior label. The establishment that imports and distributes must, however, ensure that its name and registration number is provided to the transplant establishment in order to complete the transplant establishment's records.

## Quarantine (Section 34 of the CTO Regulations)

> Quarantine — cells and tissues
> **34.** (1) A source establishment must ensure that cells, except islet cells, and tissues are quarantined until all of the following processing activities are completed:
> (a) the donor is found to be suitable after completion of the donor suitability assessment;
> (b) except in the case of fresh skin, bacteriological test results are reviewed and found to be acceptable, if applicable; and
> (c) all processing records are reviewed for completeness and compliance with the standard operating procedures.

> Additional requirement — live donors of tissue
> (2) In addition to the requirements set out in subsection (1), the source establishment must quarantine tissues that are retrieved from live donors in accordance with section 17.2 of the tissue standard.

Quarantine refers to the identification of cells and tissues that do not / have not yet met the screening and testing requirements of the CTO Regulations, and the preventative measures used to keep them from being distributed or used in transplantation. In addition, cells and tissues that are implicated in any error, accident or adverse reaction investigation must also be quarantined until the results of the investigation have determined that the cells and tissues are safe for transplantation.

Quarantine includes the storage of such cells or tissues in an area clearly identified for such use, or other procedures to prevent the release of these products for transplantation (e.g., segregation may be achieved through physical separation or through electronic identification and control systems). Quarantine does not require physical segregation of such products if the risk of cross contamination and improper release is effectively managed.

Fresh skin and other fresh tissue grafts are exempt from the requirement that tissues be quarantined until bacteriological test results are reviewed and found to be acceptable. Fresh tissue graft are exempted from this requirement to address the fact that the storage time frames for fresh grafts may not be of sufficient duration to allow for the review of bacteriological test results prior to release for transplantation. Likewise, since bacteriological testing is not a requirement under the CTO Regulations for lymphohematopoietic cells, an establishment that voluntarily performs bacteriological testing of lymphohematopoietic cells is not required to follow section 43 (1) (b) of the CTO Regulations.

In cases where tissue donated by living donors is going to be stored, the tissue must be held in quarantine for at least 180 days, at which time the donors shall be retested for the following infectious disease markers before the tissues is released (Section 17.2.2 of the tissue standard):

i. anti-HIV-1 and anti-HIV-2;
ii. anti-HBc, IgG and IgM
iii. antibodies to hepatitis C virus (anti-HCV)
iv. anti-HTLV-I and anti-HTLV-II for viable, leukocyte-rich tissues

Tissue that is not considered leukocyte-rich include, bone, cartilage, corneas, ligaments, sclera, skin, tendons and amniotic tissue.

If the initial testing performed on a living donor blood specimen includes NAT for HIV-1 and HCV, the 180 day quarantine and testing of a repeat blood sample is not required for any of the required infectious disease agents under 17.2.1 of the tissue standard, as per section 17.2.2 of the tissue standard.

## Storage (Sections 35 to 39 of the CTO Regulations)

Storage limits

**35.** An establishment that distributes cells, tissues or organs and that stores cells, tissues and adjunct vessels that were not used at the time of transplantation of the organ with which they were retrieved must observe scientifically based maximum storage periods.

A maximum storage period must be determined for each CTO to ensure its integrity, function and sterility is maintained throughout its shelf life. Factors that should be considered when establishing the expiration date for each CTO include the following, as applicable:

a) method of preservation (e.g., cryopreservation, lyophilisation or dehydration);
b) storage conditions (e.g., room temperature, refrigeration, freezing) ;
c) packaging (e.g. ability to maintain sterility and moisture content).

The maximum storage period is considered scientifically based if it meets one or more of the following criteria:

a) the storage period for specific storage conditions has been established in standards developed by recognized professional organizations, based on established practice;
b) data is available in the scientific literature to support the storage period for the specific storage conditions;
c) the storage period for the specific storage conditions has been validated by the establishment.

Establishments should provide instructions on corrective actions to be taken when temperatures rise or fall beyond the acceptable temperature limits.

Storage location

**36.** An establishment that distributes cells, tissues or organs must store them in a location that has appropriate environmental conditions that maintain their safety and that is secure against the entry of unauthorized persons.

All CTO must be stored under defined and controlled environmental conditions. The appropriate environmental conditions for storing CTO must be defined in an SOP. Documentation that the CTO were maintained under the appropriate environmental conditions must be kept and available upon request.

Environmental parameters for storage, such as temperature and humidity, must be controlled and should be monitored using calibrated monitoring devices. The documented evidence of the monitoring of these parameters must be maintained. Temperature monitoring probes or devices should be located at points that represent extreme temperature areas, as determined by a temperature mapping study, if applicable. If the storage area has an alarm system with audible signals, alarm activation points should be set at temperatures that allow time for appropriate corrective actions before the CTO reach unacceptable temperatures. The alarm warning should signal in a location that is continually monitored or staffed so that corrective action can be taken immediately.

There must be written procedures describing the actions to be taken in the event of deviations from established storage criteria. Such an event must be appropriately investigated and documented.

Access to storage areas must be restricted to designated personnel. Where physical quarantine areas are used, they must be marked appropriately, with access restricted to designated personnel. Where electronic quarantine is used, electronic access must be restricted to designated personnel.

Storage during transportation

**37.** An establishment that ships cells, tissues or organs must ensure that they are stored during transportation in appropriate environmental conditions.

This section applies to all establishments that ship CTO.

The appropriate environmental conditions for shipping CTO must be defined in a procedure. When specified, controls for temperature, light, etc. must be in place. Documentation that the CTO were maintained under the appropriate environmental conditions must be kept and available upon request.

If an establishment accepts returns of a CTO with the intent of returning the products to inventory, a process must be in place, which includes all necessary documented procedures and defined acceptability criteria that will give the establishment assurance that the CTO have been maintained under appropriate storage conditions, and that their integrity has not been compromised. This process must be defined in the establishment's SOP and must include the following documented evidence: that the CTO was maintained under appropriate conditions, that the integrity of the packaging material and the labels were not compromised, that there was no evidence of contamination or tampering and, that the unopened CTO package was free of damage. Any CTO without a label cannot be shipped or accepted by an establishment.

Segregation — tissues

**38.** An establishment that stores tissues must ensure that those that are intended for autologous use are segregated from those intended for allogeneic use.

Tissues for autologous use must be segregated from tissues for allogeneic use during storage to prevent the unintended distribution or release of autologous tissue for allogeneic use. Segregation also helps to increase the likelihood that autologous tissues receive the special handling and tracking they require, as tissues for autologous use may not have been processed according to the same standards as tissues intended for allogeneic use.

Autologous tissues must be clearly labelled as such and stored separately in restricted areas that ensure their segregation from allogeneic tissue.

Segregation may be achieved most effectively by storing allogeneic and autologous tissues in different storage equipment. If autologous and allogeneic tissues are to be stored in the same storage equipment, the storage areas for each within the storage unit must be physically separated and clearly labelled as such, in order to allow tissues intended for autologous use to be distinguished from tissues that are for allogeneic use.

> Segregation — transmissible disease agents and markers
>
> **39.** An establishment that stores cells, tissues or organs must ensure that any of them that are untested or for which the results of tests on donor blood samples are positive or reactive for transmissible disease agents or markers or are unavailable are segregated from all other cells, tissues and organs.

All CTO must be clearly labelled and stored separately in restricted areas, or controlled by a system that ensures the segregation of CTO that have been tested and deemed suitable for release/distribution from all other CTO, such as:

- CTO that are untested, or that are quarantined prior to the completion of testing for transmissible disease agents or markers, and
- CTO that are found to be unsuitable for use, unsafe, recalled and/or tested positive or reactive for transmissible disease agents or markers.

The actions taken and the final status related to each CTO must be recorded.

## Exceptional Distribution (Sections 40 to 42 of the CTO Regulations)

> Conditions
>
> **40.** A source establishment may distribute cells, tissues or organs that have not been determined safe for transplantation if all of the following conditions are met:
> (a) a cell, tissue or organ that has been determined safe for transplantation is not immediately available;
> (b) the transplant physician or dentist, based on their clinical judgement, authorizes the exceptional distribution; and
> (c) the transplant establishment obtains the informed consent of the recipient.

Given the urgent and life-saving/life-enhancing nature of transplantations, it is recognized that in exceptional circumstances, a CTO may be needed for transplantation, and a compatible CTO may be available but has yet to be deemed safe for transplantation as required by the CTO Regulations. For this reason, these Regulations provide a mechanism, referred to as "exceptional distribution", to allow for the distribution of CTO that may not meet all of the requirements of the CTO Regulations when no fully compliant CTO is available.

The intent of these Regulations is to maximize the safety of CTO used in transplantation, not to determine the suitability of a CTO for a specific recipient. For CTO to be deemed "safe" under the CTO Regulations, all of the requirements of these Regulations must have been met. There are circumstances, such as using a Hepatitis C positive CTO in a Hepatitis C positive recipient, where a CTO may be suitable, even if under these Regulations this CTO has not been deemed "safe". Other similar situations occur when, for example, not all the information from the donor screening questionnaire is available, but the use of the CTO is acceptable given the direness of the intended recipient's situation. In these situations, the suitability of a CTO is a matter of clinical discretion and/or judgement. For this reason, exceptional distribution from a source establishment requires that the transplant physician authorize the use of the CTO, and that the recipient give their informed consent for that use. Recipient consent should be obtained according to applicable provincial laws and standards of practice.

Notice in source establishment's records

**41.** (1) A source establishment that distributes cells, tissues or organs under section 40 must keep a copy of the notice of exceptional distribution in its records.

Notice in transplant establishment's records

(2) The transplant establishment must keep a copy of the notice of exceptional distribution in its records.

Contents of notice

(3) A notice of exceptional distribution must contain all of the following information:

(a) the name of the transplanted cell, tissue or organ;
(b) the provisions of these Regulations with which the cell, tissue or organ is not in compliance at the time of its distribution;
(c) the justification for the distribution that formed the basis for the transplant physician's or dentist's decision to authorize it;
(d) the name of the source establishment that distributed the cell, tissue or organ;
(e) the name of the transplant establishment and of the transplant physician or dentist who authorized the distribution; and
(f) the time and date of the written authorization of the distribution and a copy of the authorization signed by the transplant physician or dentist.

The above section requires a source establishment to put a notice of exceptional distribution in their records whenever a CTO that has met any of the exclusion criteria or transmissible disease testing requirements of the CTO Regulations is distributed. Similarly, these Regulations require that a notice of exceptional distribution be put in the transplant establishment records. The notice of exceptional distribution must contain the information stipulated under subsection 41(3) of these Regulations.

Although the notice must state the provisions of these regulations that were not met, the source establishment must also ensure that all the information has been provided to the transplant establishment in order to obtain an informed consent from the recipient.

Follow-up

**42.** A source establishment that distributes a cell, tissue or organ under section 40 before the donor suitability assessment is complete must, after the distribution, complete the assessment, carry out any other appropriate follow-up testing and notify the relevant transplant establishment of the results.

It should be noted that, according to section 42, a source establishment that has not completed the donor suitability assessment, and distributes a CTO under the conditions of exceptional distribution, must complete the assessment and carry out any other appropriate follow-up testing after distributing the CTO. The CTO Regulations also require that the source establishment notify the relevant transplant establishment of the results.

In the event that results from infectious disease testing were not available prior to exceptional distribution and transplantation, and upon receipt the results indicate the unexpected presence of infectious disease agents in the donor, establishments must report this as an accident and take the actions that are prescribed in sections 44 and 51of the CTO Regulations.

# Errors, Accidents and Adverse Reaction Investigation and Reporting (Sections 43 to 54 of the CTO Regulations)

Required action

**43.** (1) Subject to subsection (2), an establishment that is not a source establishment and that has reasonable grounds to believe that the safety of a cell, tissue or organ that is or was in its possession has been compromised by the occurrence of an error or accident during processing must immediately take all of the following steps:

(a) determine the donor identification codes of all implicated cells, tissues and organs;
(b) identify and quarantine any other implicated cells, tissues and organs in its possession; and
(c) notify the following establishments:
  (i) the relevant source establishment, and
  (ii) if the cells, tissues or organs were imported, the establishment that imported them.

Exception — importers

(2) If the establishment that receives a notice under subsection (1) is the establishment that imported the implicated cells, tissues or organs, it only has to notify the source establishment.

Contents of notice

(3) The notice must include all of the following information:

(a) the reasons for the establishment's belief that the safety of cells, tissues or organs has been compromised;
(b) an explanation of how the safety of the implicated cells, tissues or organs may have been compromised, if known;
(c) the donor identification codes of all implicated cells, tissues and organs; and
(d) the name of any suspected transmissible disease or disease agent, if known.

Written notice

(4) If the notice is given verbally, a confirmatory written notice must be sent as soon as possible afterwards.

## The following requirements apply to establishments other than a source establishment that discover or suspects that an error/accident has occurred during processing

The CTO Regulations require that these establishments report to the source establishment and to the importer (if applicable) without delay, all known or suspected errors or accidents that are associated with the CTO that are or were in its possession if they occurred during processing. They must identify all the CTO implicated in the error or accident. All the implicated CTO must be quarantined so as to prevent the transplantation or further distribution of implicated CTO. The source establishment and the importer are identified on the exterior label as required under section 33 of these Regulations.

## The following requirements apply to importers

Upon receipt of the notice under subsection 43(1), if the importer believes, based on all available information, that there are reasonable grounds to believe that the safety of the implicated CTO that are or were in its possession has been compromised by the occurrence of an error or accident during the processing, it must quarantine all implicated CTO (if still in its possession). The importer must also notify the source establishment as set out under section 43. The written notice should be sent by the next business day.

Action by source establishment

**44.** (1) A source establishment that has reasonable grounds to believe that the safety of cells, tissues or organs for whose processing it is responsible has been compromised by the occurrence of an error or accident during processing must immediately take all of the following actions:

(a) quarantine any implicated cells, tissues and organs in its possession;

(b) send a notice described in subsection (2) to all of the following establishments:

(i) if the cells, tissues or organs were imported, the establishment that imported them,

(ii) any source establishment from which it received the donor referral, if applicable,

(iii) any source establishment to which it made a donor referral, if applicable, and

(iv) any establishment to which it distributed implicated cells, tissues or organs; and

(c) initiate an investigation into the suspected error or accident.

Contents of notice

(2) The notice must include all of the following information:

(a) the reasons for its belief that the safety of the cells, tissues or organs has been compromised;

(b) an explanation of how the safety of the implicated cells, tissues or organs may have been compromised, if known;

(c) the donor identification codes of all implicated cells, tissues and organs;

(d) the name of any suspected transmissible disease or disease agent, if known; and

(e) a statement requiring all implicated cells, tissues and organs to be quarantined immediately and until further notice from the source establishment and specifying any other corrective action that must be taken.

The following requirements apply to source establishments.

A source establishment **that has reasonable grounds to believe**, based on its own information and the information received under section 43, that the safety of CTO for which it is responsible for processing (done by itself or done by another establishment on its behalf), has been compromised by the occurrence of an error or accident during processing, must immediately take the actions listed under subsection (1). The processing, in respect of CTO, means any of the following activities: donor screening; donor testing; donor suitability assessment; retrieval, except for organs and islet cells, testing and measurements performed on the CTO after they are retrieved; preparation for use in transplantation, except for organs; preservation; quarantine; banking; and packaging and labelling.

It is expected that a source establishment will notify all known establishments which received the implicated CTO within the same business day by telephone if it has reason to believe that the implicated CTO poses any danger to potential recipients. Written notices are expected to be emailed or faxed by the next business day. The source establishment must quarantine implicated CTO in a manner as described under section 39 and secured from all other compliant CTO.

When no investigation necessary

**45.** If, on receipt of a notice under subsection 43(1), the source establishment does not have reasonable grounds to believe that an investigation is necessary, it must notify the establishment to that effect in writing and provide its reasons for the decision not to conduct an investigation.

In the case that a source establishment, based on notification received under section 43 and with all available information, **has no reasonable grounds to believe** that the safety of CTO for which it is responsible for processing has been compromised by the occurrence of an error or accident during processing, it must include within its records a detailed rationale for the decision, as set out under subsection 59 (h) of the CTO Regulations. A follow-up must be provided to all establishments that contacted the source establishment regarding the suspected error and accident in order to inform them of the decision made and of the appropriate actions to be undertaken regarding the quarantined CTO.

Action on receipt of notice

**46.** An establishment that is not a source establishment and that receives a notice under section 44 or a copy of such a notice under this section must immediately take both of the following actions:

(a) quarantine all implicated cells, tissues and organs in its possession; and

(b) forward a copy of the notice to every establishment to which it distributed implicated cells, tissues or organs.

Required action

**47.** (1) Subject to subsection (2), an establishment that is not a source establishment and that has reasonable grounds to believe that an unexpected adverse reaction has occurred must immediately take all of the following steps:

(a) determine the donor identification codes of the transplanted cells, tissues or organs;

(b) identify and quarantine any other cells, tissues and organs in its possession that could potentially cause an adverse reaction in the same way as the transplanted cells, tissues or organs; and

(c) notify the following establishments:

(i) the relevant source establishment, and

(ii) if the cells, tissues or organs were imported, the establishment that imported them.

Exception — importers

(2) If the establishment that receives a notice under subsection (1) is the establishment that imported the implicated cells, tissues or organs, it only has to notify the source establishment.

Contents of notice

(3) The notice must include all of the following information:

(a) a description of the adverse reaction;

(b) the donor identification codes of all implicated cells, tissues and organs; and

(c) the name of any suspected transmissible disease or disease agent, if known.

Written notice

(4) If the notice is given verbally, a confirmatory written notice must be sent as soon as possible afterwards.

**Establishments other than source establishments** that discover or suspect that an unexpected adverse reaction has occurred must report to the source establishment and the importer (if applicable) all suspected or known unexpected adverse reactions associated with a CTO without delay. In order to comply with this requirement, the establishment must clearly identify the CTO in question. In addition, where there are other implicated CTO (for example from the same donor) in the establishment's possession, they must be identified and quarantined.
Upon receipt of the notice under subsection 47(1), an **importer** of a CTO is required to notify the source establishment of the adverse reaction.

An **unexpected** adverse reaction following the transplantation of a CTO includes the **unintended** and **unforeseen** transmission of any bacterial, viral, fungal or parasitic infection (infectious disease or disease agents), as well as malignancies or any other disease/disorders (e.g. allergy, genetic disorder, immunological disorder etc.) that is suspected to originate from the donor. These must be reported to the source establishment and importer, if applicable.

Subsection 47(3) of the CTO Regulations require that the notice include a description of the adverse reaction. This description should be as detailed as possible, in order to aid in the investigation of the adverse reaction. The donor identification codes of the implicated CTO and, where applicable, the name of the disease or disease agent suspected to have been transmitted must be included in the notice as well.

Given the time sensitive nature of the reporting of unexpected adverse reactions suspected to be associated with CTO, it is acceptable to provide the initial notice verbally. Thereafter, a written notice must be issued as soon as possible, preferably by the next business day.

It should be noted that reporting is not required when the transmission of a disease/disorder is expected, (i.e. when the infectious disease or disease agent was known to be present in the donor prior to transplantation). For example, if a bilateral lung recipient develops Mycoplasma hominis pneumonia and the donor's tracheal/bronchial aspirate was known to contain Mycoplasma hominis . In this case the Mycoplasma hominis was a known respiratory commensal in the donor therefore, pneumonia due to this bacteria, in the immunocompromised recipient was not an unexpected adverse reaction. If the donor's tracheal/bronchial aspirate was not tested or not found to contain Mycoplasma hominis (it is a difficult organism to culture), then it would be an unexpected adverse reaction and subject to reporting and investigation.

Adverse reaction reporting applies to all CTO including those distributed via exceptional distribution. The requirement to report an adverse reaction for an exceptionally distributed CTO will depend on whether the reason for exceptional distribution would lead one to expect the adverse reaction or not (i.e., can it be considered an unexpected adverse reaction).

For specific details on the unexpected serious adverse reactions that the source establishment must report to Health Canada, please see CTO regulation Section 51.

Action by source establishment

**48.** (1) A source establishment that has reasonable grounds to believe that an unexpected adverse reaction has occurred that involves cells, tissues or organs for whose processing it is responsible must immediately take all of the following actions:

(a) quarantine any implicated cells, tissues and organs in its possession;
(b) send a notice described in subsection (2) to all of the following establishments:
  (i) if the implicated cells, tissues or organs were imported, the establishment that imported them,
  (ii) any source establishment from which it received the donor referral, if applicable,
  (iii) any source establishment to which it made a donor referral, and
  (iv) any establishment to which it distributed implicated cells, tissues or organs; and
(c) initiate an investigation into the adverse reaction.

Contents of notice

(2) The notice must include all of the following information:
(a) a description of the nature of the adverse reaction;
(b) an explanation of how the safety of the implicated cells, tissues or organs may have been compromised, if known;
(c) the donor identification codes of all implicated cells, tissues and organs;
(d) the name of any suspected transmissible disease or disease agent, if known; and
(e) a statement requiring all implicated cells, tissues and organs to be quarantined immediately and until further notice from the source establishment and specifying any other corrective action that must be taken.

**Source establishments** that discover or suspect that an unexpected adverse reaction has been associated with a CTO must take action as outlined in section 48 of these Regulations. All implicated CTO in the control of the source establishment must be quarantined. A notice, as described in subsection 48 (2) of these Regulations, must be issued to all parties listed. The description of the unexpected adverse reaction should include a detailed narrative listing the consequences and outcomes experienced by the patient.

The source establishment must begin an investigation into the unexpected adverse reaction. This investigation should, at a minimum, include the information being requested in the notice. Section 51 of these Regulations further describes the investigation.

An **unexpected** adverse reaction following the transplantation of a CTO includes the **unintended** and **unforeseen** transmission of any bacterial, viral, fungal or parasitic infection (infectious disease or disease agents), as well as malignancies or any other disease/disorders (e.g. allergy, genetic disorder, immunological disorder etc.) that is suspected to originate from the donor.
It does not include the transmission of an infectious disease or disease agent where such transmission is expected. For example, the transmission of HCV from a donor that was known to be HCV positive prior to transplantation to an HCV negative recipient would not be an unexpected adverse reaction, as this would be an expected outcome resulting from the use of an organ known to be HCV positive In the case where the recipient develops HCV following transplantation of an organ that was not known to be HCV positive, such an outcome would be considered an unexpected adverse reaction.

Subsection 48(2) of the CTO Regulations require that the notice include a description of the adverse reaction. This description should be as detailed as possible, in order to aid in the investigation of the adverse reaction. The donor identification codes of the implicated CTO and, where applicable, the name of the disease or disease agent suspected to have been transmitted must be included in the notice as well.

Given the time sensitive nature of the reporting of adverse reactions suspected to be associated with CTO, it is acceptable to provide the initial notice verbally. Thereafter, a written notice must be issued as soon as possible, preferably by the next business day.

For specific details on the unexpected serious adverse reactions that must be reported to Health Canada by the Source Establishment, please see CTO regulation Section 51.

> Action on receipt of notice
> **49.** An establishment that is not a source establishment and that receives a notice under section 48 or a copy of such a notice under this section must immediately take both of the following actions:
> (a) quarantine all implicated cells, tissues and organs in its possession; and
> (b) forward a copy of the notice to every establishment to which it distributed implicated cells, tissues or organs.

**These requirements apply to establishments other than a source establishment that receive a notice under section 48 of the CTO Regulations.** Section 49 of these Regulations state that an establishment that is not a source establishment and that receives a notice under section 48 must quarantine all implicated CTO over which it has control. It also requires that a copy of the notice received must be sent to all establishments to which it has sent implicated CTO.

> Requirement to cooperate
> **50.** An establishment must provide the source establishment that is conducting an investigation with any relevant information in its possession with respect to cells, tissues or organs that it distributed or transplanted.

All establishments contacted by a source establishment conducting an investigation must assist in the investigation and provide all relevant information to the source establishment without delay. This includes, but is not limited to, an inventory list of implicated CTO with their disposition (number and type processed, distributed, transplanted, quarantined, and destroyed), the names of establishments to which the implicated CTO have been distributed and details regarding the adverse reaction. Requests for information made to establishments by the source establishment often reflect requests that are made to the source establishment by Health Canada.

Reports to Minister

**51.** (1) A source establishment that is conducting an investigation into either of the following subject-matters must provide the Minister with the reports described in subsection (2):

(a) a suspected error or accident that is identified after distribution of cells, tissues or organs that could lead to a serious adverse reaction involving the transmission of an infectious disease or disease agent; and

(b) an unexpected serious adverse reaction that is thought to involve the transmission of an infectious disease or disease agent.

Contents and timing

(2) The reports must include the following information and be provided at the following times:

(a) within 24 hours after the start of the investigation, a preliminary report that includes all relevant information that is available at that time; and

(b) within 15 days after the start of the investigation and every 15 days after that until the final report is made, an update on any new information about the suspected error or accident or serious adverse reaction, on the progress made in the investigation during those 15 days and on the steps taken to mitigate further risks.

## Reporting Errors, Accidents and Adverse Reactions

In the context of these Regulations, the Minister is represented by the Health Canada's Biological Product Compliance Program (BPCP) under the Regulatory Operations and Regions Branch (RORB) for reports of a suspected error or accident that is identified and the Marketed Health Products Directorate (MHPD) for reports of a serious unexpected adverse reaction that is thought to involve the transmission of an infectious disease or disease agent.

When a source establishment has reason to suspect that an unexpected serious adverse reaction has occurred that involves the transmission of an infectious disease or disease agent by a transplanted CTO, the source establishment must report to Health Canada all available information regarding the unexpected serious adverse reaction, within 24 hours.

When a source establishment has reason to suspect that an error or accident has occurred that could lead to a serious adverse reaction involving the transmission of an infectious disease or disease agent, the source establishment must report to Health Canada all available information regarding the suspected error or accident, within 24 hours. Only those errors and accidents that are identified after the distribution of affected CTO must be reported to Health Canada at the following address: hc.bpcp-pcpb.sc@canada.ca.

The information provided in this report could include, but is not be limited to, the name of the suspected infectious disease and/or disease agent, the description of the CTO, the number of recipients potentially affected, and the identification code of the donor(s) (if available at the time).

This requirement to report to Health Canada does not supersede the establishment's requirement to report designated infectious diseases to public Provincial/Territorial Health Authorities.

If the source establishment has reported an adverse reaction and during the course of the investigation discover that an error or accident is the cause of the adverse reaction, the E/A also needs to be reported to BPCP. Likewise, if the source establishment has reported an E/A and during the course of the investigation discover that an unexpected serious adverse reaction has resulted from the E/A, the unexpected serious adverse reaction also needs to be reported to MHPD.

## Clarification Regarding Accident Reporting:

Clarification regarding the circumstances under which certain test results that are received post-transplant must be reported as an accident to Health Canada:

- With respect to blood cultures, source establishments are expected to report to Health Canada cases of positive blood cultures indicative of an active/acute infection of clinical significance. For example, sepsis is a clear contraindication to donation and a source establishment would only be able to distribute organs from a septic donor under the Exceptional Distribution provisions if the results were available prior to distribution. A positive blood culture result received post-transplant that was indicative of sepsis would be considered an unexpected result, thus meeting the definition of an accident. Alternatively, some localized infections identified by positive urine and sputum cultures might be considered "expected" and therefore it would not be necessary to report such positive results received post-transplant to Health Canada as accidents.
- With respect to the reporting of positive donor toxoplasmosis test results in heart donors, source establishments are not required to report positive toxoplasmosis test results to Health Canada, whether or not they are received pre or post-transplant. Instances of positive test results are not considered unexpected due to the prevalence of toxoplasmosis in the general population. Therefore, positive toxoplasmosis donor test results that are received post-transplant do not constitute an accident under the CTO Regulations and are not required to be reported to Health Canada. The same logic applies to positive CMV and EBV donor test results.
- All test results must be forwarded to the transplant programs and any other source establishments responsible for processing other cells and tissues from the same donor.

Clarification regarding the circumstances under which certain test results that are received post-transplant should be reported as an accident to Health Canada:

- The presence of any bacteria or fungi in the blood of a donor could be clinically significant to the health outcome of the recipient. In the absence of a protocol to determine clinical significance, all unexpected positive blood cultures (i.e., received post-transplant), should be reported. This reporting could be reduced if the establishment were to develop protocol(s), in consultation with experts in microbiology and transplant transmissible diseases, to differentiate between:
  (a) positive blood cultures indicative of bacteremia or fungemia versus those that likely resulted from contamination of the blood specimen during handling of the specimen;;
  (b) bacteremia or fungemia that are clinically significant versus those that are not.
- If protocol(s) described in (a) above were implemented, Health Canada would only expect the establishment to report unexpected positive blood cultures that were indicative of bacteremia or fungemia.
- If protocol(s) described in (a) and (b) above were implemented, Health Canada would only expect the establishment to report unexpected positive blood cultures that were indicative of bacteremia or fungemia and considered clinically significant.
- Regardless, the establishment should immediately report all positive blood culture results, received post-transplantation, to the transplant establishment. This permits the transplant establishment to assess the clinical significance to the organ recipient and to provide timely medical treatment, if necessary.

Tissue transplant establishments that perform microbial testing prior to transplantation shall inform source establishments as per section 43 if the culture results are indicative of an active/acute infection of clinical significance.

Not all situations must be reported, for example, in the case of ocular tissues, if the eye bank received a report that a positive bacteria result has been found by another source establishment for a particular donor but the bacteria would be considered acceptable (not be an active infection of clinical significant for ocular tissue), this would not be reportable to Health Canada.

## Error and Accident Reporting (directed to BPCP)

All establishments must send their reports to: hc.bpcp-pcpb.sc@canada.ca.

A link to the error and accident report form "Human Cells, Tissues and Organs for Transplantation - Error or Accident Preliminary Investigation Report Form (FRM-0172)" can be found on the Health Canada Web site. This report form should be used for reporting to BPCP.

## Investigation

During an investigation, a source establishment is to determine whether any other CTO are affected, and the status of the implicated CTO (the number of CTO processed, distributed, quarantined, transplanted and destroyed and the number of establishments contacted). Source establishments are to consider whether any additional tests are required (e.g., donor testing, archived serum sample testing, bacteriological testing). Testing results must meet the requirements of the CTO Regulations. A protocol is to be developed to describe the interpretation of laboratory results. Criteria are to be developed for acting on positive (reactive) results.

Any documentation pertaining to the investigation must be available for review by Health Canada upon request.

## Reports

Every 15 calendar days after the start of the investigation, and until the final report is submitted, the source establishment is to provide the BPCP with an update on any new information about the suspected error or accident, on the progress made in the investigation during those 15 days, and on the steps taken to mitigate further risks, including root cause analysis and planned corrective actions. The updates are to include information regarding the number of CTO processed, distributed, quarantined, transplanted and destroyed and the number of establishments contacted.

The Minister may request a recall based on the information received. A recall is a set of actions taken by an establishment to remove a product (CTO) from the market which represents a health risk for Canadians or which otherwise contravenes the F&DA.

At any time during the investigation, Health Canada can request additional information as set out under section 14 of these Regulations.

If a source establishment can determine before the start of an investigation that no CTO affected by the error or accident has been exported to Canada, it does not need to report it to the Minister. However, it is recommended that the establishment inform the Minister that an error, an accident or an adverse reaction involving CTO not exported to Canada has taken place, so as to avoid miscommunications.

If it is determined during the course of the investigation that a CTO involved in the error or accident was exported to Canada, the establishment must provide to the Minister all reports described in sections 51 and 54 of the CTO Regulations.

## Reporting Unexpected Serious Adverse Reactions

When a Source Establishment has reason to suspect that an unexpected serious adverse reaction has occurred that involves the transmission of an infectious disease or disease agent from the donor to the recipient by transplanted CTO, the source establishment must report to Health Canada all available information regarding the unexpected serious adverse reaction, within 24 hours of starting the investigation.

Source Establishments are encouraged to voluntarily report other unexpected serious adverse reactions such as the transmission of malignancies, or any other disease/disorders (e.g. allergy, genetic disorder, immunological disorder etc.) that are thought to originate from the donor of the transplanted CTO.

### Information on preliminary (initial), follow-up and final reports

The preferred Mandatory Adverse Reaction Form for Industry is available on the Health Canada Web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/mandatory-adverse-reaction-reporting-form-industry.html. This form should be used for the preliminary (initial) report as well as any follow-up reports to the MHPD.

### Preliminary (Initial) Report

Pursuant to section 51(2)(a) of the Regulations[1], within 24 hours of the start of an investigation, the source establishment must report to MHPD any required risk mitigation measures that it undertook with respect to the unexpected serious adverse reaction, as well as all other relevant information that is available at the time. This information should include, but is not limited to:

- the identification code of the donor(s) (if known);
- the date of CTO retrieval from the donor;
- the transplantation date;
- the date and description of the adverse reaction;
- the suspected infectious disease and/or disease agent,
- the implicated CTO; and
- the distribution of CTO from the implicated donor.

If there is more than one affected recipient associated with a single donor, one reporting form for each affected recipient is required. Each affected recipient should be represented by a unique Source Establishment Report Number.

### 15-Day Update Reports (Follow-up Reports)

Pursuant to section 51(2)(b) of the Regulations[1], within 15 days after the start of the investigation and every 15 days after that until the final report is submitted, the Source Establishment must provide MHPD with an update on the status of the investigation and any further risk mitigation measures taken. This update should also include relevant clinical information (e.g., progress/outcome of the patient and other implicated recipients, results of laboratory investigations) as well as information regarding the identification of the root cause of the infection (e.g., evidence of a causal association to the donor or how donor transmission was excluded, actions taken).

All updated information on the reporting form should be clearly marked and the steps taken as part of the investigation should be presented in chronological order. Additional pages may be attached to the Mandatory Adverse Reaction Reporting Form for Industry if more space is needed.

At any time following the receipt of an adverse reaction report, the MHPD may request additional information as set out under section 14 of the CTO Regulations. Should this information be in the possession of an establishment other than the source establishment, the former is required to collaborate, as set out under section 50 of the CTO Regulations.

### Contact information

Adverse reaction reports from Source Establishments to the Minister covered by this guidance document should be sent to the Canada Vigilance Program of the MHPD. The preferred method of submitting adverse reaction reports is by **fax**:

Canada Vigilance Program
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Tunney's Pasture
Address Locator: 1908C
Ottawa, Ontario
K1A 0K9
Fax: 613-957-0335
E-mail for enquiries: HC.canadavigilance.cto.SC@canada.ca

When investigation shows no contamination or compromise

**52.** (1) If the results of the investigation show that the implicated cells, tissues or organs are not contaminated or compromised, the source establishment must notify every establishment that was notified under section 44 or 48 to that effect in writing and that they may be released from quarantine.

Forwarding of copies of notice

(2) On receipt of a notice under subsection (1), an establishment that is not a source establishment must forward a copy of the notice to every establishment to whom it distributed implicated cells, tissues or organs.

Where it is determined that the implicated CTO are not contaminated, the CTO may be distributed. The source establishment should prepare a list containing the identification codes of all CTO that were declared not contaminated. The source establishment must then notify, in writing, all the establishments that were previously notified under section 44 or 48 of the CTO Regulations that the CTO with the identification codes specified in the list may be distributed. The source establishment may distribute the CTO in its possession that have the identification codes specified on the list.

When investigation inconclusive or shows contamination or compromise

**53.** (1) If the results of the investigation show that some or all of the implicated cells, tissues or organs are contaminated or compromised, or the results are inconclusive, the source establishment must notify every establishment that was notified under section 44 or 48 to that effect in writing and that they may not be released for distribution.

Forwarding of copies of notice

(2) On receipt of a notice under subsection (1), an establishment that is not a source establishment must forward a copy of the notice to every establishment to whom it distributed implicated cells, tissues or organs.

Where it is determined that the CTO are contaminated or the results are inconclusive, the implicated CTO are to be destroyed or reserved for distribution under exceptional distribution as stated under section 40 of the CTO Regulations. The source establishment is to prepare a list containing the identification codes of the CTO that are contaminated or where the results of the investigation are inconclusive. It must also notify all establishments that were previously notified under section 44 or 48, in writing, that all implicated CTO having the identification codes specified on the list must be quarantined and are considered unsafe for transplantation. The source establishment is to destroy the implicated CTO in its possession, except if they are reserved for distribution under exceptional distribution. All establishments that received a notification must follow the directions on handling of the implicated CTO.

Final report to Minister

**54.** (1) On completion of an investigation, the source establishment must submit a detailed final report to the Minister that contains at least all of the following information:

a) the results of the investigation;
b) the final disposition of the cells, tissues and organs that were the subject of the investigation and the reasons for that disposition; and
c) any corrective actions taken.

Summaries of final reports

(2) The source establishment must send a summary of the final report to every establishment that was notified under section 44 or 48.

Forwarding of summaries

(3) An establishment that receives a summary under subsection (2) must send a copy of it to every establishment to which it distributed implicated cells, tissues or organs.

Upon completion of the investigation, the source establishment is to notify and provide a final report to the BPCP or MHPD, as appropriate. The final report provided is to be detailed and is to indicate the results of the investigation; it should include conclusions, specify any infectious agent(s), results of any tests performed, follow-up and corrective actions taken, and details of the reconciliation of the CTO and their final disposition (number processed, distributed, transplanted, quarantined, destroyed).

### Other requirements

All E/A and AR must be investigated and documented by the source establishment regardless of the reporting obligation to Health Canada.

Under subsection 59(h), a source establishment is required to keep records of any errors, accidents and adverse reactions associated with CTO it has processed or transplanted, and any corrective action taken. In addition, the source establishment must keep the records of its investigation along with the assessment and monitoring as set out under subsection 59(h).

Under subsection 60(f), a transplant establishment is required to keep records of any errors, accidents and adverse reactions associated with CTO it has transplanted, and any corrective action taken.

Furthermore, establishments are required under subsection 74(2) to review any SOP based on the receipt, from the source establishment, of a summary report of an error, accident investigation or a follow up report to an adverse reaction investigation that revealed a deficiency.

## Records (Sections 55 to 63 of the CTO Regulations)

Record quality

**55.** Records kept by an establishment must be accurate, complete, legible and indelible.

Records (with the exception of distribution records) must identify the person performing the activities carried out and the dates of the various entries. Establishments must have a system in place to ensure the accuracy of their records, including the manual transcription of test results in cases where no source data is available. Transcribed data must be independently verified.

The records must be retained in a comprehensible and accessible form and any hand written entry of information must be made using indelible ink. A cross-out is to be used for correction of text in a paper document. Any correction, entry of information, or notation made after the original date of record completion must be initialled or signed, and dated in such a way as to allow a reader to differentiate between the original and amended information.

One standardized format for dates (e.g., YYYY/MM/DD or MM/DD/YY) should be used for all records.

Records shall be maintained in a manner to preserve their completeness and accuracy over time and must be accessible when needed. Establishments may decide to use microfiche, microfilm or other means of retaining permanent records. Records must be accessible at all times. The establishment must verify the transfer of information to microfiche, microfilm or other media used to retain information. The accuracy of the transfer of information should be verified by an individual other than the individual who transferred the information.

**Guiding principles for the transfer to secondary medium and destruction of original records**

Transfer

The transfer process **should** be validated and documented in appropriate procedures, and ensure that:

a. Measures are in place to verify that the transfer is accurate and done by appropriately trained individuals (e.g. attestation or certification of copies by a person not involved in the transfer);
b. Corrections to the original data can be clearly captured in the secondary medium.; and
c. Process follows existing standards when possible (i.e., Canadian General Standard Board).

Where records are copied off-site, a contract signed by the establishment and the service provider must detail specific requirements such as those for transport to that site, copy quality, storage conditions, and, where relevant, destruction of original documents.

Electronic or Other System

The format and system where documents are retained **should** also be validated for its intended use and include the following:

d. Design to ensure the tracing of any alterations and updates, if permitted, such as source, date, and content (i.e., audit trail);
e. Back-ups at regular intervals;
f. Security measures in place and documented to protect against data corruption, whether through accidental deletion, equipment failures, material deterioration, or a variety of other hardware and software problems;
g. Controlled access to appropriate individuals (through use of passwords for example);
h. Plan in place for future accessibility (in light of changes over time in technology, personnel, or third-party contractors); and
i. Location of records that permits immediate access to records.

Destruction of original records

The destruction of original paper records following their transfer to a secondary medium may be acceptable with the principles discussed in this document in place. In addition, the process to describe the destruction of the original paper records **should** be documented in appropriate procedures. Considerations should be given to additional requirements that may apply to the destruction of personal/confidential information.

Other considerations

Other requirements may apply to the transfer, storage and destruction of records, including:

a. Provincial (for example, medical records)

b. Institutional
c. Legal requirements (e.g., transfer to an electronic format may not be acceptable when it contains a watermark or official seal)

Donor identification code — source establishment
**56.** (1) A source establishment must assign a donor identification code to each donor of a cell, tissue or organ for which it has responsibility.
Donor identification code — all establishments
(2) Every registered establishment and transplant establishment must ensure that the donor identification code is a component of its records system.

The donor identification code is an identifier, assigned by a source establishment, that corresponds uniquely to all CTO from that donor processed by, or on behalf of the given source establishment. The donor identification code will associate the CTO with information about the donor from which it was retrieved. Depending on how many CTO were retrieved, a donor may have more than one donor identification code associated with them. This is because the source establishment may be different for various types of CTO retrieved from the donor, and all source establishments must assign a donor identification code to every donor it is responsible for processing.

For example, in the case of a multiple tissue/organ donor, where bone, ocular tissue, kidney and liver were to be retrieved from the donor, an ODO would be the source establishment responsible for the processing and safety of the organs and therefore would assign a donor identification code to the organs. Similarly, the tissues might be sent to a comprehensive tissue bank for processing and this tissue bank would assign a donor identification code to the tissues that it processes from that donor. Thus the donor would be associated with two different donor identification codes. If however, the bone and ocular tissues were sent to a bone and an eye bank rather than a comprehensive tissue bank, then each of these establishments and the ODO would assign a donor identification code, and so the donor would be associated with three different identification codes.

Health Canada recognizes that having one identification code per donor might be preferable. However, there are generally different source establishments for each of the different types of CTO, located in different provinces, regions and countries, the logistics of having one identification code per donor would be extremely difficult; it would require the collaboration of all of the individual programs to create a single donor coding system, or the establishment of a single national organ and tissue donation body.

Even though it is not currently possible to have a single identification code for every CTO donor at this time, it is still necessary that each CTO be associated with information about the donor from which it was retrieved, and any processing activities that it underwent. For this reason, subsection 56(2) of the CTO Regulations requires that the donor identification code be a component of the record keeping system used by all registered and transplant establishments.

A source establishment may assign other numbers or codes to a CTO in addition to the donor identification code, for the purposes of their own record keeping, however; all identifiers must be traceable to the original donor. Likewise, other establishments involved in the processing of a CTO may also assign their own numbers or codes to that CTO for their records. For this reason, under sections 30 to 32 of the CTO Regulations, the donor identification code must be clearly labelled as such. This will ensure that everyone that handles a CTO will be able to identify and record the donor identification code that was assigned by the source establishment.

Requirement

**57.** An establishment's records must contain information with respect to all cells, tissues and organs that it processes, distributes, imports or transplants that identifies
(a) the establishment from which it receives the cells, tissues and organs; and
(b) all establishments to which it distributes the cells, tissues and organs.

Records must contain information about the establishment from which CTO are received and establishments to which CTO are distributed. Requiring each establishment to record this information maintains traceability throughout the chain of distribution. In addition to the name of each establishment, records should include the following information:

- identity of each CTO received or distributed, by the donor identification code and other attributes with the corresponding date;
- information from the retrieval establishment that identifies the donor;
- the establishment address;
- the establishment phone and fax numbers;
- contact information in case of an emergency;
- an emergency phone number; and
- the establishment registration number, if applicable.

Shipping documents

**58.** An establishment's records must include all shipping documents with respect to cells, tissues and organs that it ships to another establishment.

Source establishment records

**59.** The source establishment must keep records with respect to cells, tissues and organs that it processes that contain at least all of the following information:
(a) the donor identification code;
(b) documentation showing completion of the donor suitability assessment;
(c) a description of the cells, tissues and organs retrieved from the donor;
(d) if applicable, the name of any source establishment from which it received a donor referral or to which it made a donor referral;
(e) the name of the retrieval establishment;
(f) documentation of all processing activities;
(g) the notice of exceptional distribution, if any; and
(h) documentation of any reported errors, accidents and adverse reactions and their investigation, if any, in connection with cells, tissues or organs retrieved from the donor that it banked or distributed and any corrective action taken.

It is not necessary that traceability information be contained in the donor chart, but it is to be contained in records kept by the source establishment.

Records are a critical component of any Quality Assurance (QA) system. They are documented evidence of compliance, and must be maintained concurrently with the performance of each significant step in the processing, importation, storage, distribution (including exceptional distribution), transplantation and investigation of error and accident and adverse reaction of each CTO so that all steps can be clearly associated with the person, time/date and location of such activities.

Aside from other recording requirements that are covered under various sections of this document, the following requirements are specific to processing activities.

### Processing equipment records:

Records must be maintained for each piece of equipment that could affect the quality and the safety of the CTO. These records must include, but are not limited to the following:

- identity of the equipment;
- serial number or other unique identifier;
- manufacturer's name and contact information;
- date the equipment was received, put into service, and if applicable, out of service;
- manufacturer's instructions, if available, or reference to their retention;
- equipment performance records that confirm the equipment's suitability for use (equipment qualification), including calibration and/or verification records (which should incorporate such information as dates of tests, test results, adjustments made, acceptance criteria and frequency of checks);
- schedules of completed and anticipated maintenance activities;
- any damage, malfunction, modification or repair, of the equipment;
- usage log sheet; and
- records of recall.

The records should be readily available for the life span of the equipment. Each item of equipment should be uniquely labelled, marked or otherwise identified.

### Testing records:

Source establishments must have records which indicate that all laboratory testing of transmissible disease markers are performed in accordance with the corresponding test kit manufacturer's instructions.

Where applicable, records of written agreement between the source establishment and any testing laboratory should be in place to provide relevant information, including:

- the appropriate tests performed for each sample;
- a stipulation that the laboratory is to follow the manufacturer's instructions and perform the tests within the limits and time frames suggested by the manufacturer;
- a stipulation that the test kits used to test donors for the transmissible disease agents comply with these Regulations;
- a current test kit list and notification upon test kit changes;
- testing validation data; and
- the method of reporting results to source establishment and an interpretation of the results.

For testing laboratories, detailed testing records, logs and other supporting documents should be readily accessible to the source establishment, as required, and should include the following:

- the name of the test kit;
- the lot number;
- the name, lot number and expiry date of the solutions and reagents used;
- the expiry date;
- the name of the manufacturer;
- testing validation data; and
- records of recall, if applicable.

## Critical supplies records (e.g. devices, instruments, reagents, containers):

Records must be maintained for each critical supply item that is used during processing and that could affect the quality and the safety of the product. These records include, but are not limited to the following:

- identity of the supply, including type, lot number;
- manufacturer's name
- expiration date, if applicable (obtain clarification from the manufacturer in cases where the date is unclear);
- manufacturer's instructions, if available; and
- records to demonstrate that non-disposable instruments used in the processing are cleaned, disinfected and/or sterilized to prevent contamination and cross-contamination according to written procedures.

Where applicable, records of written agreement between the source establishment and the retrieval establishment must be maintained to provide relevant information such as roles and responsibilities of the parties involved. The written agreement should also include an attestation that they are in compliance with the CTO Regulations.

If an error, an accident or an adverse reaction occurs, a report must be written that describes the incident, the investigation, corrective actions taken, and any follow-up activities required.

In addition to the donor identification code, other attributes such as a description of the CTO must be unique to avoid any possible mix-up of their identity (e.g., Achilles Tendon L and Achilles Tendon R).

In the case of a source establishment, documentation of a notice of exceptional distribution as described in subsection 41(3) of the CTO Regulations must be available in its records. Similarly, follow-up assessment and testing results of the donor are to be available in the source establishment's records.

Transplant establishment records

**60.** The transplant establishment must keep records with respect to cells, tissues and organs that it transplants that contain at least all of the following information:

(a) a description of the transplanted cells, tissues or organs;
(b) the donor identification code;
(c) the registration number of the source establishment;
(d) the notice of exceptional distribution, if any, and confirmation that the donor suitability assessment was completed as required by section 42;
(e) information that allows the identification of the recipient; and
(f) documentation of any errors, accidents and adverse reactions and their investigation in connection with those cells, tissues or organs and any corrective action taken.

It is not necessary that traceability information be contained in the recipient chart, but it is to be contained in records kept by the transplant establishment.

Records are a critical component of any QA system. They are documented evidence of compliance, and must be maintained concurrently with the performance of each significant step in the processing, importation, storage, distribution (including exceptional distribution), transplantation and investigation of error and accident and adverse reaction of each CTO so that all steps can be clearly associated with the person, time/date and location of such activities.

In addition to the donor identification code, other attributes such as a description of the CTO must be unique to avoid any possible mix-up of their identity (e.g., Achilles Tendon L and Achilles Tendon R).

In the case of exceptional distribution, a copy of the notice of exceptional distribution must be available in the transplant establishment's records. Documentation of follow-up assessment and testing must also be available in the transplant establishment's records.

Establishments to cooperate

**61.** An establishment must provide the source establishment and the transplant establishment with all of the information described in sections 59 and 60, respectively, that it possesses to complete the establishment's records

When two or more establishments are involved in CTO related activities, the relationship and responsibilities of each must be delineated in writing and that documentation must be maintained at each establishment.

Furthermore, establishments that are contacted by a source establishment or a transplant establishment for any information described in sections 59 and 60 of the CTO Regulations must provide that establishment with all the information requested.

Retention — 10 years after transplantation

**62.** (1) An establishment must keep the following records for at least 10 years after the date of transplantation, if known, or for at least 10 years after the date of distribution, final disposition or expiry of the cell, tissue or organ, as the case may be, whichever is the latest:

(a) the records described in section 57;
(b) the records described in section 59, except paragraph (h);
(c) the records described in section 60, except paragraph (f); and
(d) the record of destruction or other disposition of the cell, tissue or organ, if applicable.

Retention — 10 years after record creation

(2) An establishment must keep the following records for 10 years after the date of their creation:

(a) the records described in paragraphs 59(h) and 60(f); and
(b) reports of audits conducted under section 76, if applicable.

Retention — employee records

(3) An establishment that distributes cells, tissues or organs must keep records of the qualifications, training and competency of its employees for 10 years after the time an individual ceases to be an employee of the establishment.

Retention — standard operating procedures

(4) An establishment that distributes cells, tissues or organs must keep a copy of every version of its standard operating procedures for 10 years after they are superseded by a new version.

With the exception of subsections 59(h) and 60(f), processing activity records, as well as records of importation, distribution and transplantation of the CTO that the establishment has in its possession must be kept in the following manner:

If the establishment knows the date of transplantation: the records must be kept at least 10 years after the date of transplantation.
If the establishment does not know the date of transplantation, the record must be kept at least 10 years after the expiry date, the date of the final disposition or the date of the final distribution of the CTO, as the case may be, whichever is the latest.

Records maintained under subsections 59(h) and 60(f) must be kept for 10 years from the date of their creation. Other records described in section 62 of the CTO Regulations are to be kept for 10 years from the date of the employee's departure from the establishment (subsection 3) or the date that the version of the SOP was superseded by a new version (subsection 4).

Storage of records

**63.** An establishment that distributes cells, tissues or organs must store records in a location that has appropriate environmental conditions and that is secure against the entry of unauthorized persons.

Record storage areas must maintain the integrity of the records. Access to the storage area must be restricted to designated personnel.

Where records are stored off-site, an SOP must detail specific requirements such as those for transport to that site, copy quality, storage conditions, document retrieval, and, where relevant, destruction of original documents.

## Personnel, Facilities, Equipment and Supplies (Sections 64 to 69 of the CTO Regulations)

Sufficient number and qualifications

**64.** (1) An establishment that distributes cells, tissues or organs must have sufficient personnel who are qualified by education, training or experience to perform their respective tasks to carry out the establishment's activities.

Competency

(2) An establishment that distributes cells, tissues or organs must have a system for the orientation and training, both initial and ongoing, of personnel and for the evaluation of their competency.

Shortage of personnel or underqualified staff increases the risk of errors and accidents. A sufficient number of qualified personnel must be available to perform the tasks required.

An establishment should prepare and maintain a current organizational chart with clear delineation of lines of responsibility. Job descriptions must describe the qualifications and functions of each staff position.

Personnel must receive initial and ongoing training appropriate for their duties. Training programs must be available and must include evaluation of competency. The assessment of competency may include:

- direct observation of performance;
- monitoring of recording and reporting;
- written tests to assess problem-solving skills;
- assessment of knowledge of operating procedures and theory; and
- for personnel who normally perform routine testing, assessment of performance in proficiency tests.

Personnel affected by a new or revised SOP must receive training regarding the new or revised SOP. Training records must include information necessary to verify that individuals have been trained. This could include the signature of the employee and the date on which this training was conducted. Employees must receive training prior to performing any tasks associated with a new or revised SOP and confirmation of training must be documented. If technical training or competency testing is required, training records must also reflect this information.

Records of the qualifications, training and continuing competency of individuals must be maintained.

Requirements

**65.** The facilities of an establishment that distributes cells, tissues or organs must be constructed and maintained to permit all of the following:
(a) the carrying out of all of its activities;
(b) the efficient cleaning, maintenance and disinfection of the facilities in a way that prevents contamination and cross-contamination;
(c) environmental and microbiological monitoring and control appropriate to the areas where its activities are carried out; and
(d) controlled access to all areas where its activities are carried out.

Premises must be located, designed, constructed and adapted to suit the activities to be carried out. Their design and furnishing must minimize the risk of errors and accidents and microbiological contamination. Premises should be designed so that operations can proceed in an orderly manner.

Facilities must be designed to allow for their effective decontamination and to prevent cross-contamination during the movement of personnel and materials between different areas.

The sanitation program should include the following:

- cleaning requirements applicable to all areas with emphasis on processing areas that require special attention;
- the list of products for cleaning and disinfection, along with the manufacturer's instructions;
- the responsibilities of any outside contractor;
- disposal procedures for waste material and debris;
- pest control measures;

There must be controlled access to all areas where aseptic activities are conducted and where products and samples are stored.

Establishments should have microbial and environmental monitoring procedures with alert and action limits in areas where aseptic activities are conducted and susceptible products are processed or packaged.

There must be no direct access from the areas where processing is carried out to the exterior of the building, except for emergency purposes.

Requirements — equipment

**66.** An establishment that distributes cells, tissues or organs, in carrying out its processing and storage activities, must use equipment that is cleaned and maintained and, whenever applicable,
(a) qualified for its intended purpose;
(b) calibrated;
(c) disinfected or sterilized before each use; and
(d) requalified or recalibrated, as appropriate, after any repair or change is made to it that results in a change to its specifications.

All equipment must be located in a way that facilitates cleaning and maintenance. Cleaning must be performed according to established schedules to prevent contamination, cross-contamination or spread of infectious diseases. The cleaning procedure must be validated to ensure the removal of contaminants and cleaning product residues that could interact with the CTO. Where possible, equipment must be disinfected or sterilized using validated methods to reduce the risk of contamination and cross-contamination.

Where applicable, equipment must be qualified and/or calibrated according to the manufacturer's instructions, to ensure they consistently operate within established tolerance limits. Equipment maintenance, recalibration and requalification must also be performed according to the manufacturer's instructions.

For additional information on equipment, see section 5.3 of the general standard.

Requirements — storage equipment

**67.** An establishment that distributes cells, tissues or organs that uses equipment to store cells, tissues or adjunct vessels that are not used immediately in organ transplantation must ensure that the equipment maintains appropriate environmental conditions.

All CTO must be stored according to conditions described on the label. When specified on the label, controls for temperature, humidity, light, etc. must be in place. Documentation that the CTO were maintained under the appropriate environmental conditions must be maintained.

Environmental parameters for storage, such as temperature and humidity, must be controlled and should be monitored using calibrated monitoring devices. Temperatures and/or liquid nitrogen levels shall be recorded at defined intervals and records documenting the monitoring of these parameters must be maintained. Temperature monitoring probes or devices should be located at points that represent extreme temperature areas, as determined by a temperature mapping study. If the storage area has an alarm system with audible signals, alarm activation points should be set at temperatures that allow time for appropriate corrective actions before the CTO reach unacceptable temperatures. The alarm warning should signal in a location that is continually monitored or staffed so that corrective action can be taken immediately.

Procedures describing the actions to be taken in the event of deviations from established criteria must be written. Such events must be appropriately documented and investigated.

Processing supplies

**68.** An establishment that processes cells, tissues or organs must use qualified supplies for those activities that could affect the safety of the cells, tissues or organs, and must store solutions, reagents and other supplies under appropriate environmental conditions.

The person responsible for the establishment's QA (the medical director, the scientific director or their respective designate) must establish acceptance criteria for the supplies used in the processing of CTO.

Supplies should be quarantined until the person in charge of QA finds each specific lot is acceptable for use. The conditions of use and storage of each supply must be appropriate as instructed by the manufacturer. The expiry dates of supplies and ongoing storage conditions must be strictly observed.

Cleaning supplies

**69.** An establishment that processes cells, tissues or organs must ensure that it uses supplies for cleaning, maintenance, disinfection or sterilization that do not react with, or that are not absorbable by, the cells, tissues or organs.

The choice of cleaning supplies used in the processing areas should be reviewed to ensure that they do not have any negative effects on the quality and safety of the CTO that they come in contact with. The cleaning supplies must be of the appropriate grade and quality.

Cleaning supplies that could affect the safety of the CTO are to be used or stored according to the manufacturer's instructions or as stated on the label. They must not generate toxic vapours or degradation products that could contaminate the CTO.

The name and the lot numbers of supplies that are used to clean, disinfect or sterilize equipment and instruments should be recorded and the expiry dates must be strictly observed.

## Quality Assurance System (Sections 70 to 76 of the CTO Regulations)

Application
**70.** Sections 71 to 76 apply only to establishments that distribute cells, tissues or organs.

Under these Regulations, all registered importers, establishments that distribute as intermediaries and source establishments must have a QA system (refer to section 71 below for details). This includes source establishments that are also transplant establishments i.e. in the case of the lymphohematopoietic cells that are not banked and organs from living donors.

Quality assurance system required
**71.** An establishment must ensure that it has a quality assurance system in place that complies with the requirements of these Regulations for all activities that it carries out.

A QA system must be established in order to support the objective of ensuring the maximum quality and safety of the CTO distributed by the establishment. QA consists of all the organized arrangements made and the measures taken to reach this objective.

### The QA system must have the following elements:

Management requirements (sections 71 to 76)

- The establishment has a QA system in place, which is defined, documented, implemented, maintained and kept up to date.
- The establishment has an organizational structure that defines and documents personnel responsible for any activities under these Regulations.
- Policies, processes and procedures are available to cover all the activities (sections 72 to 75 of the CTO Regulations).
- The senior management is responsible for the establishment to attain its quality objective.
- The QA policies, processes, programs, procedures and instructions must be documented and communicated to all relevant personnel. The establishment's management must ensure that the documents are understood by personnel and implemented.
- Satellite facilities must be operated in accordance with the establishment's QA system.

Documentation system (including sections 72 to 75)

- Document Control: the establishment shall define, document and maintain procedures to control all documents and information that form its quality documentation system.
- Records: the establishment must have a system to ensure that all documents required under the CTO Regulations are retained and stored as described under section 62 and 63.
- All documents relevant to the QA system must be uniquely identified and shall be clear, concise and written in a consistent format, and according to establishment policies.
- All documents are controlled so that only the current version of SOPs and policies are available for use, and the expired versions are not in circulation.

A system for employing qualified personnel and providing on-going personnel training (see section 64);

A system or program for the security and maintenance of the establishment's facilities (see section 65);

Equipment (see section 66)

Computer Systems/Data processing control that are used in the processing and distribution of CTO and other regulated activities

- Processes must be in place for authorizing and documenting modifications to the computer system.
- Policies must be established which define who may use the computer, who may access recipient/donor data and who is authorized to enter and change results or data, or modify computer programs. There should be processes and procedures to support the maintenance and security of computer systems.

Process Control

- The establishment must ensure that processes are carried out under controlled conditions, according to written procedures prepared by qualified personnel (sections 72 to 75)
- Change Control: any changes to the processes, materials, equipment and facilities that may impact the quality and safety of CTO must be reflected in the written procedures and approved before being implemented.
- Changes to SOPs corresponding to section 72 must be approved according to subsection 73 (d) of the CTO Regulations.

Quality Control

- The establishment must have processes and procedures to monitor and control the quality and safety of the CTO, as applicable.

Suppliers for Critical Supplies and Services (See section 68)

- Establishments must have policies, processes, and procedures (such as agreements and audits), to evaluate the ability of suppliers of critical materials and services to consistently meet specified requirements.

Errors and Accidents and Adverse Reactions Reporting, and Investigations (described in sections 43 to 54).

- There must be an errors, accidents and adverse reaction management system to ensure they are identified, recorded, reported, evaluated, investigated, and followed.
- Corrective action must be approved and implemented when required.
- Each establishment must maintain a system of control that permits a complete and rapid recall of any CTO that has been distributed, when required.

Audit program (see section 76).

## The QA system should have the following elements:

Preventive action

- Procedures for preventive action should include: analysis of data, including trend- and risk-analyses, and monitoring of effectiveness. If preventive action is required, action plans should be developed, implemented and monitored to reduce the likelihood of the occurrence of non-conformance and to take advantage of the opportunities for improvement.

Customer Complaints and Corrective Actions

- The facility should have a policy and procedures for the investigation and handling of complaints.

Standard operating procedures required
72. An establishment must have standard operating procedures with respect to the safety of cells, tissues and organs for all activities that it carries out.

All activities that could affect the safety and quality of CTO must be described in written SOPs that have been approved by the medical director, the scientific director or their respective designate. These SOPs must be considered part of the establishment records pertaining to the processing, distribution and importation of CTO.

For example, such SOPs could be in place for the following activities:

- processing;
- label control and verification;
- final safety assessment of CTO, storage, distribution, importation;
- record keeping, adverse reactions and errors and accident reporting and notification;
- investigation of errors, accidents and adverse reactions;
- recall;
- facility cleaning and maintenance and environmental monitoring; and
- maintenance, cleaning, calibration and qualification of equipment and instruments, if applicable;
- exceptional distribution; and
- personnel training.

SOPs provide personnel with instructions or directions so that activities are performed and documented consistently and in compliance with regulatory requirements.

Requirements
73. The standard operating procedures must meet all of the following requirements:
(a) be in a standardized format;
(b) be approved by the medical director or scientific director;
(c) be available for use at all locations where the relevant activities are carried out;
(d) have any changes to the procedures approved by the medical director or scientific director before being implemented; and
(e) be kept up-to-date.

The format of each SOP is to indicate, at a minimum, the following:

- the type of procedure;
- the title and purpose of the procedure;
- the unique number identifying the document;
- the date that the SOP became effective and the date(s) that it was revised;
- the signature of the authorizing person (the medical director, scientific director or designate) and the date of authorization;
- on each page, the page number (of the total number of pages);
- a clear outline of steps and instructions to be followed in the described procedure which matches the details in the processing records (e.g., worksheets, forms or computer screens), if applicable;
- staff categories responsible for performing all or part of the steps in the SOP; and
- references to publications cited in support of the policies and procedures.

The issuance of SOPs and any changes must be maintained by a document control system that ensures that the SOP is current and authorized by the medical director, the scientific director or their respective designate. In an urgent situation, a change to a current operating procedure is allowed if permitted by the medical director or the scientific director and the change is signed and dated. The reason for the change from the procedure must be documented. Invalid or obsolete documents must be promptly removed to prevent their inadvertent use.

Routine review

**74.** (1) An establishment must review its standard operating procedures every two years and again after any amendment to these Regulations.

Supplementary review

(2) An establishment that receives a summary of a final report of an error, accident or adverse reaction investigation or the report of an audit either of which reveals a deficiency in a standard operating procedure must review that procedure.

SOPs must be reviewed and/or revised every two years at a pre-determined period, by a knowledgeable person(s). Documentation that the review occurred must be available. SOPs must also be amended to reflect any relevant changes introduced by amendments to the CTO Regulations. Revisions must be approved by the medical director, the scientific director or their respective designate and documentation must be available that the review has occurred. The reason for any revision should be documented.

All SOPs must be retained for reference and inspection for 10 years after they are superseded by a new version, as set out under subsection 62(4) of the CTO Regulations.

Records of compliance

**75.** An establishment must keep records that demonstrate that it has implemented its standard operating procedures.

Records must indicate the dates when SOPs are initially implemented as well as when revised versions of SOPs are implemented.

Audits

**76.** An establishment must conduct an audit every two years of the activities that it carries out to verify that those activities comply with these Regulations and with its standard operating procedures, by a person who does not have direct responsibility for the activities being audited.

Audits are required to ensure that all regulated activities are performed according to the CTO Regulations and the establishment's SOPs. Audits must be performed according to an established program and must address regulated activities that have an impact on CTO safety. All the activities that need to be audited must be reviewed at a minimum on a two-year basis. An SOP should be written for such audit activities. The findings from audits and follow-up actions required must be documented and reviewed by the management. Follow-up actions / corrective actions should be implemented in a timely manner.

Audits should be performed by personnel who are responsible for carrying out the QA system requirements. Personnel conducting audits must be knowledgeable in the subject matter and the process being audited. The management of the establishment must define the responsibilities and authority of the audit. In addition, personnel auditing an activity must not be directly responsible for that activity. For example, a supervisor responsible for donor screening must **not** audit any donor screening activities done in its own facility.

Any establishment that has an arrangement with another establishment to perform any regulated activity on its behalf is responsible for verifying, on a two-year basis, that those activities are being conducted appropriately and are in compliance with the CTO Regulations.

For example, the establishment can assess a contractor's compliance by performing an audit of the contractor or by reviewing audit reports that are provided by the contractor or a third party that has performed an audit of the contractor.

Health Canada recommends that the living donor organ programs work together to develop standardized SOPs and questionnaires to help ensure consistency with respect to donor screening and testing practices amongst the different organizations. In this case internal audits could be shared amongst establishments as a means of fulfilling the audit requirements under section 76 when the donor assessment is performed by another establishment on behalf of the transplant establishment.

While Health Canada recommends that an establishment audit all establishments that perform regulated activities on its behalf, an establishment that contracts another establishment to perform transmissible disease testing on its behalf is not required to audit the testing facility if the following criteria are met:

- They have an agreement in place that stipulates that the testing lab will inform the source establishment of any changes regarding the assays used to perform the required tests.
- The source establishment maintains an up to date list of the assays used on its behalf.
- The testing facility is accredited by a recognized laboratory accreditation program and the source establishment has a copy of the current accreditation certificate. Examples include provincial programs such as the Institute for Quality Management in Healthcare (IQMH) program or an international program such as the College of American Pathologists (CAP) Laboratory Accreditation Program.
- The testing lab follows all appropriate test kit package inserts as well as its own SOPs and if any deviations occur during the testing, informs the source establishment of these deviations

## Powers of Inspectors (Section 77 of the CTO Regulations)

Taking photographs

77. An inspector may, in the administration of these Regulations, take photographs of any of the following:
    (a) any article that is referred to in subsection 23(2) of the Act;
    (b) any place where the inspector believes on reasonable grounds that any article referred to in paragraph (a) is processed; and
    (c) anything that the inspector believes on reasonable grounds is used or is capable of being used in the processing of any article referred to in paragraph (a).

An inspector is a person designated under section 22(1) of the F&DA for the purpose of enforcement of the Food and Drugs Act and Regulations. The intent of this section is that, once designated by the Minister, an inspector will carry out his/her responsibilities in accordance with the guiding principles of transparency and fairness, as described in Policy 001. Inspectors' regulatory powers are described under section 23 of the F&DA.

Section 23 authorises inspectors to examine and make copies of documents and records, regardless of whether they contain personal medical information. These documents are reviewed for the purpose of verifying compliance with the CTO Regulations. Health Canada handles all information in accordance with applicable laws on privacy, confidentiality and access to information. Further information can be found on the Health Canada Access to Information and Privacy Division website.

## Transitional Provisions (Section 78 of the CTO Regulations)

Processed within 5 years before registration

78. (1) Subject to subsection (2), the following establishments may import, distribute or transplant, as the case may be, cells and tissues that were processed within five years before the day on which these Regulations are registered:

(a) a registered establishment; and

(b) a transplant establishment that does not distribute cells or tissues.

Prohibition

(2) An establishment may not import, distribute or transplant, as the case may be, cells or tissues under subsection (1) unless the requirements of subsection 56(2) and section 57 are met.

## Coming into Force (Section 79 of the CTO Regulations)

Six months after registration

79. (1) These Regulations, except subsection 26(1), come into force six months after the day on which they are registered.

Exception

(2) Subsection 26(1) comes into force one year after the day on which these Regulations are registered.

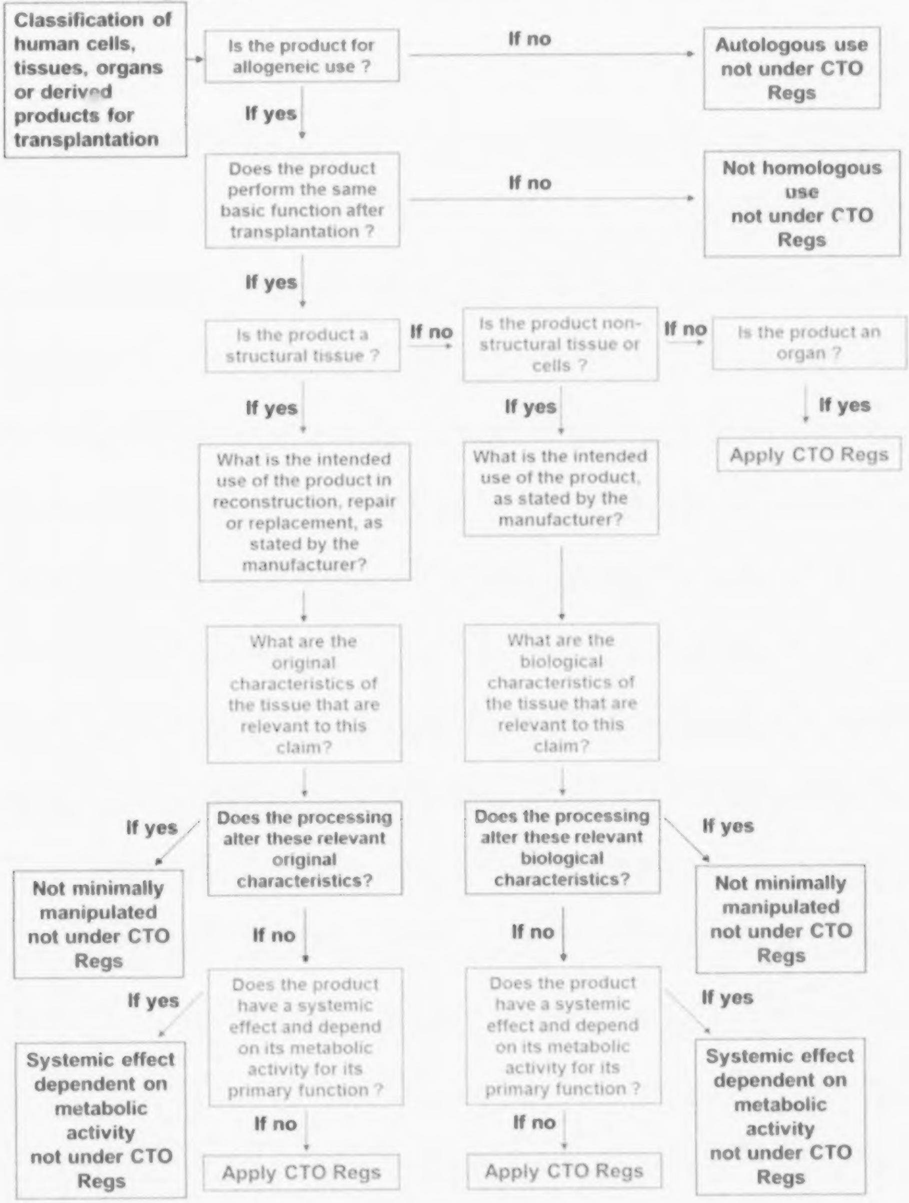
Transitional provision

(3) Section 78 ceases to be in force five years after the day on which these Regulations are registered.

# Appendices

## Appendix 1: Decision Tree for Help in the Classification of CTO

Note that, despite having a systemic effect and being dependent on their metabolic activity for their primary function, minimally manipulated lymphohematopoietic cells and islet cells that are intended for homologous use are regulated under the CTO Regulations.


Classification of human cells, tissues, organs or derived products for transplantation
Is the product for allogeneic use ?
If no
Autologous use not under CTO Regs
If yes
Does the product perform the same basic function after transplantation ?
If no
Not homologous use not under CTO Regs
If yes
Is the product a structural tissue ?
If no
Is the product non-structural tissue or cells ?
If no
Is the product an organ ?
If yes
If yes
If yes
Apply CTO Regs
What is the intended use of the product in reconstruction, repair or replacement, as stated by the manufacturer?
What is the intended use of the product, as stated by the manufacturer?
What are the original characteristics of the tissue that are relevant to this claim?
What are the biological characteristics of the tissue that are relevant to this claim?
If yes
Does the processing alter these relevant original characteristics?
Does the processing alter these relevant biological characteristics?
If yes
Not minimally manipulated not under CTO Regs
If no
If no
Not minimally manipulated not under CTO Regs
If yes
Does the product have a systemic effect and depend on its metabolic activity for its primary function ?
Does the product have a systemic effect and depend on its metabolic activity for its primary function ?
If yes
Systemic effect dependent on metabolic activity not under CTO Regs
If no
If no
Apply CTO Regs
Apply CTO Regs
Systemic effect dependent on metabolic activity not under CTO Regs

## Appendix 2: Appropriate and effective tests for infectious disease testing

These tables are included for reference purposes only; for complete information concerning tests to be performed to assess the suitability of CTO donors, including time frames, please refer to section 18-23 of this guidance document.

**Tissue Donors, except ocular tissues**

| Appropriate and effective infectious disease markers | Mandatory | Recommended |
|---|---|---|
| anti-HIV 1 | X | - |
| anti-HIV 2 | X | - |
| HBsAg | X | - |
| anti-HBc IgG | X | - |
| anti-HBc IgM | X | - |
| anti-HCV | X | - |
| anti-HTLV-I | X* | - |
| anti-HTLV-II | X* | - |
| syphilis | X | - |
| HIV-1 using NAT | X** | - |
| HCV using NAT | X** | - |
| WNV using NAT | - | X |

* Mandatory for donors of leukocyte-rich tissue and recommended for donors of tissues that are not considered to be leukocyte-rich.

** Mandatory for tissue from deceased donors. Not necessary for tissue from living donors if the 180 day quarantine and donor retesting protocol is followed.

**Ocular tissues donors**

| Appropriate and effective infectious disease markers | Mandatory | Recommended |
|---|---|---|
| anti-HIV 1 | X | - |
| anti-HIV 2 | X | - |
| HBsAg | X | - |
| anti-HBc IgG | X | - |
| anti-HBc IgM | X | - |
| anti-HCV | X | - |
| HIV-1 using NAT | X | - |
| HCV using NAT | X | - |
| WNV using NAT | - | X |

**Organ or islet cells donors**

| Appropriate and effective infectious disease markers | Mandatory | Recommended |
|---|---|---|
| anti-HIV 1 | X | - |
| anti-HIV 2 | X | - |
| HBsAg | X | - |
| anti-HBc IgG | X | - |

| | | |
|---|---|---|
| anti-HBc IgM | X | - |
| anti-HCV | X | - |
| anti-HTLV-I | X | - |
| anti-HTLV-II | X | - |
| toxoplasmosis | X* | - |
| syphilis | X | - |
| anti-CMV IgG | X | - |
| anti-CMV IgM | - | X |
| Eipstein-Barr Virus | X | - |
| HIV-1 NAT | - | X** |
| HCV NAT | - | X** |
| WNV using NAT | - | X |

*For heart donors

** HIV-1 NAT and HCV NAT are only recommended for living organ donors and high risk deceased organ donors whose organs will be exceptionally distributed.

**Lymphohematopoietic cells donors**

| Appropriate and effective infectious disease markers | Mandatory | Recommended |
|---|---|---|
| anti-HIV 1 | X | - |
| anti-HIV 2 | X | - |
| HBsAg | X | - |
| anti-HBc IgG | X | - |
| anti-HBc IgM | X | - |
| anti-HCV | X | - |
| anti-HTLV-I | X | - |
| anti-HTLV-II | X | - |
| anti-CMV IgG | X | - |
| anti-CMV IgM | - | X |
| syphilis | X | - |
| HIV-1 using NAT | X* | X |
| HCV using NAT | X* | X |
| WNV using NAT | X | - |

*Mandatory for banked lymphohematopoietic cell donation (i.e., cord blood) only.

## Appendix 3: Revised Measures to Address the Potential Risk of Zika Virus Transmission through Human Cells, Tissues and Organs

**Issued: May 5, 2016**

The purpose of this notice is to provide information regarding the spread of recent Zika virus outbreaks in Mexico, the Caribbean, and Central and South America and offer guidance to the cell, tissue and organ donation and transplantation communities regarding measures to address the potential risk posed to recipients of human cells, tissue and organs. It is intended to replace the notice that was issued on February 9, 2016.

**Background:**

Zika virus is a flavivirus transmitted by Aedes mosquitoes, predominantly the Aedes aegypti species. The mosquito primarily bites during the day and is the same type of mosquito that transmits Dengue and Chikungunya[1].

Zika virus was first identified in 1947 in Uganda. There was a considerable Zika virus disease outbreak in French Polynesia in 2013. More recently, in 2015, Zika virus was recognized in Brazil and has since been spreading quickly throughout many regions of the Western Hemisphere including Mexico, the Caribbean, and Central and South America.

For up to date information on Zika affected areas, see http://www.phac-aspc.gc.ca/phn-asp/2016/zika-eng.php or http://www.cdc.gov/zika/geo/.

On Monday February 1, 2016, the World Health Organization (WHO) declared the spread of Zika virus an international public health emergency due to the temporal and geographic association with clusters of cases of congenital anomalies, mainly microcephaly, in the Western Hemisphere. On March 22, 2016, WHO held a press conference to report on recent high-level scientific meetings and concluded that sexual transmission of Zika virus does occur. Based on a growing body of preliminary research, there is now scientific consensus that Zika virus is a cause of microcephaly and Guillain-Barré syndrome[2,3]. Other neurological disorders, such as myelitis and meningoencephalitis, have also been associated with Zika virus[4,5].

When symptomatic, Zika virus infection typically causes a mild self-limiting febrile illness with symptoms such as fever, rash, joint pain, myalgias, headache and conjunctivitis. However, asymptomatic infection occurs in approximately 80% of Zika virus infected individuals[6].

Zika virus has been detected in blood donors and is believed to be transmissible through blood transfusion, similar to dengue virus[7]. Zika virus has also been detected in semen samples and cases of sexual transmission have been reported[8,9,10].

There is also concern that the virus has the potential to be transmitted by cell, tissue and organ transplantation. Zika virus RNA was detected in brain, liver, spleen, kidney, lung, and heart samples from one fatal case in an adult male with lupus erythematosus, rheumatoid arthritis, chronic use of corticosteroids, and alcoholism[11].

Based on limited available information, a potential for transmission of Zika virus by birth tissues, such as amniotic membrane, is suspected. Maternal-fetal transmission of Zika virus, most likely by transplacental transmission or during delivery, has been reported[12,13,14,15,16]. Zika virus has also been detected in placenta and amniotic fluid[17,18].

At this time, however, the seriousness of the Zika virus disease in transplant recipients is unknown. The distribution and/or infectivity of the Zika virus in the body's various cells, tissues or organs are not well understood either.

Due to the large number of North Americans travelling to affected regions, particularly during the winter months, and the potential for severe complications, particularly amongst pregnant recipients, Health Canada would like to stress the importance of obtaining donor information regarding any recent travel history to Zika affected areas and considering any recent symptoms of febrile illness in donors.

Testing for Zika virus can be arranged through consultation with the Public Health Agency of Canada (PHAC) National Microbiology Laboratory.

https://www.cnphi-rcrsp.ca/gts/faces/public/index.xhtml?lang=en

However, as there are no licensed commercial test kits available in Canada for Zika virus detection, routine donor testing is not recommended at this time.

Based on limited data, the incubation period is believed to be 3 to 14 days and viremia is thought to range from a few days to 1 week after symptom onset. The longest duration of viremia in the published literature is 11 days[19]. In Canada, a blood donor deferral period of 21 days is currently being implemented for individuals that have returned from Zika affected areas. In addition, Health Canada distributed a Notice to semen importers and processors on March 18, 2016 stating that "semen donors should be considered ineligible to donate if the donor has been diagnosed with Zika virus infection in the past 6 months or they have resided in or travelled to an area with active Zika virus transmission within the past 6 months".

**Measures to Address the Potential Risk of Zika Virus Transmission:**

Organ Donation Organizations (ODOs):
As per the requirements of the Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations) ODOs must obtain the travel history of organ donors. If this information indicates that the donor has returned from a Zika affected area in the past 21 days, then this information should be communicated to transplant teams so they can weigh the risks of potential Zika virus transmission against the benefits of organ transplantation on a case by case basis. When decisions are made to distribute organs in such cases, this should be done in accordance with the exceptional distribution provisions under sections 40 - 42 of the CTO Regulations.

It is also recommended that this approach be adopted when the donor has had sexual contact in the past 21 days with a man who is known to have had a medical diagnosis of Zika virus infection within six months prior to the sexual contact or who resided in, or travelled to, an area with active Zika virus transmission within the past six months.

Living Donor Organ programs:
Living organ donors should be advised of the risks of travelling to Zika affected areas in the weeks leading up to the donation and the implications to the safety of the organ recipient. This should include a discussion of the risks of having sexual contact within 21 days of donation with a man who is known to have had a medical diagnosis of Zika virus infection within six months prior to the sexual contact or who resided in, or travelled to, an area with active Zika virus transmission within the past six months.

In the case of living organ donors that have returned from Zika affected areas in the past 21 days, consideration should be given on a case by case basis to postponing the donation until a minimum of 21 days has elapsed since the date of the donor's departure from the affected area or from the last sexual contact with a man who is known to have had a medical diagnosis of Zika virus infection within six months prior to the sexual contact or who resided in, or travelled to, an area with active Zika virus transmission within the past six months. In such instances it is the responsibility of the transplant program to weigh the risks and benefits of postponing donation.

If the donation is not postponed, the distribution of organs should be in accordance with the exceptional distribution provisions under sections 40 - 42 of the CTO Regulations.

The same process should be followed for donors who were diagnosed with a Zika virus infection in the past 21 days or that have exhibited symptoms of Zika virus infection in the past 21 days that arose within 2 weeks of departure from an area with active transmission of Zika virus. However, in these cases, consideration should be given to postponing the donation until a minimum of 21 days has elapsed since the resolution of symptoms in the donor.

Fresh Lymphohematopoietic Cell Transplant programs:
Donors of fresh lymphohematopoietic cells should be advised of the risks of travelling to Zika affected areas in the weeks leading up to the donation and the implications to the safety of the recipient. This should include a discussion of the risks of having sexual contact within 21 days of donation with a man who is known to have had a medical diagnosis of Zika virus infection within six months prior to the sexual contact or who resided in, or travelled to, an area with active Zika virus transmission within the past six months.

As per the requirements of the CTO Regulations, lymphohematopoietic cell transplant programs are required to obtain the travel history of donors. In the event that it becomes known in the days leading up to the initiation of the recipient's conditioning regimen that the donor has returned from a Zika affected area within 21 days of the planned donation or had sexual contact within 21 days of the planned donation with a man who is known to have had a medical diagnosis of Zika virus infection within six months prior to the sexual contact or who resided in, or travelled to, an area with active Zika virus transmission within the past six months, then consideration should be given on a case by case basis to postponing the conditioning regimen and cell donation until a minimum of 21 days has elapsed since the date of the donor's departure from the affected area or the last sexual contact with an at risk male. In such instances it is the responsibility of the transplant program to weigh the risks and benefits of postponing donation.

If the donation is not postponed, the distribution of cells should be in accordance with the exceptional distribution provisions under sections 40 - 42 of the CTO Regulations.

The same process should be followed for donors who were diagnosed with a Zika virus infection in the past 21 days or that have exhibited symptoms of Zika virus infection in the past 21 days that arose within 2 weeks of departure from an area with active transmission of Zika virus. However, in these cases, consideration should be given on a case by case basis to postponing the conditioning regimen and cell donation until a minimum of 21 days has elapsed since the resolution of symptoms in the donor.

Cord Blood Banks and Tissue Banks that Process Birth Tissues:
As per the requirements of the CTO Regulations, cord blood banks are required to obtain the travel history of donors. This information, in addition to other information is necessary to determine whether there is potential risk of Zika virus transmission from the cord blood. Cord blood banks should consider donors ineligible under any of the circumstances described below. In addition, tissue banks that process birth tissues should not undertake donation of birth tissues under any of these circumstances.

1. The mother has been diagnosed with Zika virus infection at any point during that pregnancy.
2. The mother has resided in, or travelled to, an area with active Zika virus transmission at any point during that pregnancy.
3. The mother has had sex at any point during that pregnancy with a male who is known to have had a medical diagnosis of Zika virus infection within six months prior to the sexual contact or who resided in, or travelled to, an area with active Zika virus transmission within the past six months.

**Note:** Cord blood donations that are determined ineligible are not prohibited from being collected, stored and released for transplantation if done in accordance with the exceptional distribution provisions under sections 40 - 42 of the CTO Regulations.

Tissue Banks
It is recommended that tissue banks not undertake donation from individuals with a medical diagnosis of Zika virus infection in the past 6 months.

**NB: This notice is based on currently available information and may be subject to change as more information becomes available.**

Questions or comments may be submitted to the Office of Policy and International Collaboration at the address below:

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